

## Synthesis and Biological Activities of 4-Phenyl-5-pyridyl-1,3-thiazole Derivatives as Selective Adenosine A<sub>3</sub> Antagonists

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To investigate the potency of an adenosine A<sub>3</sub> receptor (A<sub>3</sub>AR) antagonist as an anti-asthmatic drug, a novel series of 4-phenyl-5-pyridyl-1,3-thiazole derivatives was synthesized and evaluated in human adenosine A<sub>1</sub>, A<sub>2A</sub> and A<sub>3</sub> receptor and rat adenosine A<sub>3</sub> receptor binding assays. From investigation of the SAR study, compound **7a** was identified as a highly potent human and rat A<sub>3</sub>AR antagonist. This compound inhibited IB-MECA-induced plasma protein extravasation in the skin of rats and showed good oral absorption. Also, compound **7a** significantly inhibited antigen-induced hyper-responsiveness to acetylcholine in actively sensitized Brown Norway rats. These results show that 4-phenyl-5-pyridyl-1,3-thiazole derivatives are potential candidates to enable the evaluation of A<sub>3</sub>AR antagonists. Further evaluation of this class of compounds may afford a novel anti-inflammatory agent such as an anti-asthmatic drug.

**Key words** 5-pyridyl-1,3-thiazole; adenosine A<sub>3</sub> receptor antagonist; antiplogistic; rat antigen-induced asthma model; Brown Norway rat

Adenosine, an endogenous purine nucleoside, modulates a variety of physiological functions in various organs and tissues, and interacts with four specific G-protein-coupled receptor subtypes (GPCRs), classified as A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>.<sup>1,2</sup> All four receptors are coupled *via* G proteins to the adenylate cyclase—cAMP signal transduction pathway. Activation of A<sub>1</sub> and A<sub>3</sub> receptors inhibits adenylate cyclase through G<sub>i</sub> coupling, while activation of A<sub>2A</sub> and A<sub>2B</sub> receptors stimulates adenylate cyclase through G<sub>s</sub> coupling.<sup>3</sup> In particular, the adenosine A<sub>3</sub> receptor (A<sub>3</sub>AR) is distributed in different organs (lung, liver, kidney, heart and brain),<sup>4</sup> and the potential therapeutic applications of antagonizing this receptor are proposed to be useful for the treatment of inflammation,<sup>5</sup> myocardial and brain ischemia,<sup>6–8</sup> and cancer.<sup>9,10</sup>

As human adenosine A<sub>3</sub> receptor (hA<sub>3</sub>AR) antagonists, many potent and selective antagonists, such as xanthine derivatives,<sup>11</sup> 1,4-dihydropyridines,<sup>12–15</sup> triazoloquinazolines,<sup>16,17</sup> flavonoids,<sup>18</sup> triazolophthalazines,<sup>19</sup> thiazolopyrimidines,<sup>19,20</sup> isoquinolines,<sup>21,22</sup> quinazolines,<sup>21</sup> pyrazolotriazolopyrimidines,<sup>23–25</sup> thiazoles and thiadiazoles,<sup>26</sup> and triazolopurines<sup>27,28</sup> have been reported as new hA<sub>3</sub>AR antagonists. Although these antagonists showed strong hA<sub>3</sub>AR antagonistic activity and good selectivity against other adenosine receptor subtypes, they were found to be weak or ineffective against rat A<sub>3</sub>AR (rA<sub>3</sub>AR),<sup>1,11,12,15,28,29</sup> and could therefore not be evaluated in rat *in vivo* models. The homology of A<sub>3</sub>AR among several species was reported and the only 72% homology between human and rat A<sub>3</sub>AR was one reason for species differences.<sup>28</sup> As selective hA<sub>3</sub>AR antagonists that showed moderate affinity to rA<sub>3</sub>AR, only MRS 1191<sup>14</sup> and MRS 1523<sup>15</sup> ( $K_i=1.42$ ,  $0.113 \mu\text{M}$ , respectively) have been reported, but these activities seemed to be insufficient for evaluation in rat models. Thus, A<sub>3</sub>AR antagonists which show equipotent affinity and selectivity in different species have been desired for pharmacological probes on animal models, and the evaluation and selection of new drugs in preclinical phase candidates is likely to be easier.

Our focus on an anti-asthmatic research program prompt-

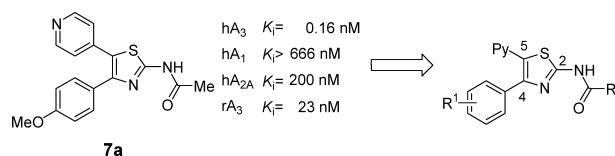


Fig. 1. Chemical Structure and Biological Profiles of Lead Compound **7a**

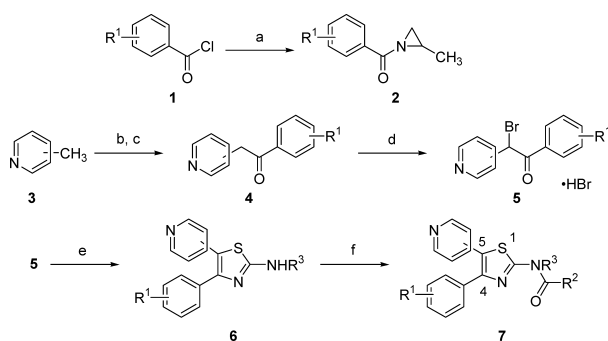
ed us to evaluate the potential of A<sub>3</sub>AR antagonist as a therapeutic target. From high throughput screening, 4-phenyl-5-pyridyl-1,3-thiazole derivative **7a** was identified as the preferable lead compound. We have already reported 1,3-thiazole derivatives as p38 MAP kinase inhibitors.<sup>30,31</sup> These compounds were bound at the ATP binding site of the kinase, and ATP is an adenosine-related compound. We therefore focused our attention on compound **7a** and investigated further. In the *in vitro* binding assay, compound **7a** showed strong hA<sub>3</sub>AR antagonistic activity ( $K_i=0.16 \text{ nM}$ ) and good hA<sub>3</sub>AR selectivity, as shown in Fig. 1. Moreover, the rA<sub>3</sub>AR antagonistic activity of this compound was moderate ( $K_i=23 \text{ nM}$ ). To evaluate the efficacy of the rat asthma model, improvement of the rA<sub>3</sub>AR antagonistic activity of **7a** was critical. In the present paper, we report the discovery of a series of 2-acylamino-4-phenyl-5-pyridyl-1,3-thiazole derivatives as novel and potent antagonists against human and rat A<sub>3</sub>AR through structural modification based on screening hit **7a**.

### Chemistry

The general approach for the several 4,5-disubstituted 2-acylamino-1,3-thiazoles **7** is outlined in Chart 1, according to the previous report.<sup>30</sup>

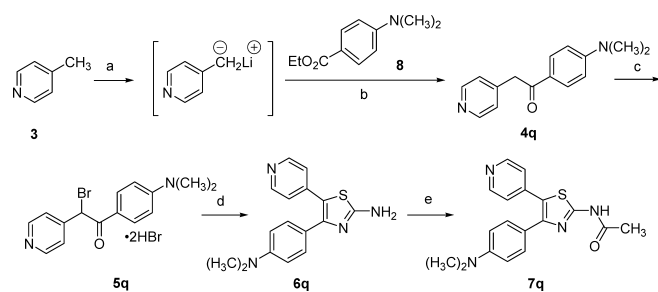
The *N*-benzoyl-2-methylaziridines **2** were prepared from the corresponding acid chlorides and commercially available 2-methylaziridine, according to the Schotten–Baumann procedure. The *N*-benzoyl-2-methylaziridines **2** were condensed with the lithium anion of methylpyridine **3** to afford the corresponding ketones **4**.<sup>30,32</sup> In this reaction, the selective lithiation at methyl proton was occurred and no product from

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Reagents: (a) 2-methylaziridine, ether, 2*N* NaOH, 0 °C; (b) LDA, hexane, THF, -78 °C then -20 °C; (c) **2**, -78 °C; (d) Br<sub>2</sub>, AcOH, 70 °C; (e) H<sub>2</sub>NC(S)NHR<sup>3</sup>, Et<sub>3</sub>N, CH<sub>3</sub>CN, 80 °C; (f) R<sup>2</sup>COCl, DMAP, DMA, 70 °C.

Chart 1. Synthesis of 2-Acylaminothiazole Derivatives (**7**)



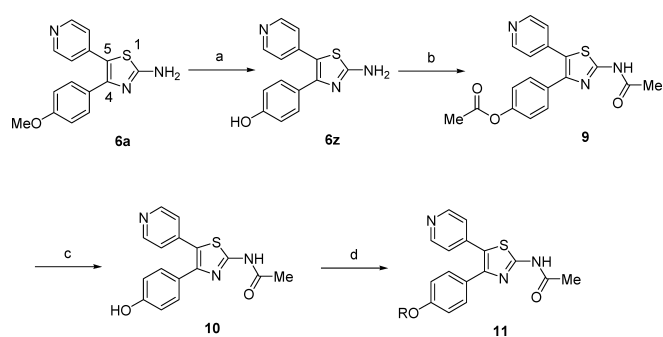
Reagents: (a) LDA, hexane, THF, -78 °C then -20 °C; (b) ethyl 4-(*N,N*-dimethylamino)benzoate **8**, -10 °C; (c) Br<sub>2</sub>, 30% HBr (aq.), AcOH, 70 °C; (d) H<sub>2</sub>NC(S)NH<sub>2</sub>, Et<sub>3</sub>N, CH<sub>3</sub>CN, 80 °C; (e) CH<sub>3</sub>COCl, DMAP, DMA, 70 °C.

Chart 2. Synthesis of 4-[4-(*N,N*-Dimethylamino)phenyl]thiazole Derivative (**7q**)

lithium anion of pyridine core was observed. Ketones **4** were brominated to give  $\alpha$ -bromoketones **5**. Cyclization of bromoketones **5** and thioureas provided 2-amino-1,3-thiazoles **6**. Acylation of 2-amino-1,3-thiazoles **6** was carried out using various acid chlorides with a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) in *N,N*-dimethylacetamide (DMA) at 70 °C.

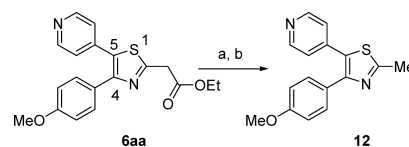
In order to obtain 4-[4-(*N,N*-dimethylamino)phenyl]thiazole derivative **7q**, we tried to take a slightly different approach as shown in Chart 2. 1-[4-(*N,N*-Dimethylamino)phenyl]-2-(4-pyridyl)ethanone **4q** was obtained from ethyl 4-(*N,N*-dimethylamino)benzoate **8** and 4-pyridylmethyllithium, which was prepared from 4-methylpyridine **3a** and lithium diisopropylamide (LDA), because of a failure to obtain 4-(*N,N*-dimethylamino)benzoyl-2-methylaziridine. Although direct bromination of ketone **4q** was unsuccessful due to the *N,N*-dimethylamino moiety, we achieved bromination using the hydrobromide salt of **4q**, which was prepared with hydrobromic acid *in situ*. Cyclization reaction of **5q** and acylation of **6q** was carried out under the same condition.

The 4-methoxyphenyl derivative **6a** was converted to 4-alkoxyphenyl derivative **11**, as shown in Chart 3. Acid hydrolysis of the methoxy group of **6a** yielded 4-hydroxyphenyl derivative **6z** and acetylation of **6z** was performed using acetyl chloride and DMAP in DMA to give diacetyl derivative **9**. Saponification of compound **9** provided 4-hydroxyphenyl derivative **10** and the alkylation of intermediate **10** using the corresponding alkyl iodide (RI) gave the alkoxy derivative **11**.



Reagents: (a) 47% HBr (aq.), reflux; (b) MeCOCl (5 eq.), DMAP, DMA, 70 °C; (c) K<sub>2</sub>CO<sub>3</sub>, rt.; (d) <sup>t</sup>BuOK, DMA, 0 °C, then alkyl iodide.

Chart 3. Synthesis of 4-Alkoxyphenylthiazole Derivatives (**11**)



Reagents: (a) 2 *N*-NaOH (aq.), rt.; (b) EtOH, reflux.

Chart 4. Synthesis of 2-Methylthiazole Derivative (**12**)

Hydrolysis of ethyl 2-thiazoleacetate **6aa** and decarboxylation provided the desired 2-methyl compound **12**, as shown in Chart 4, according to the previous report.<sup>31</sup> All of the synthesized thiazole derivatives are listed in Table 1.

## Results and Discussion

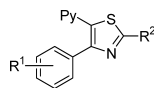
All compounds were tested in radioligand binding assays to determine their affinities for adenosine A<sub>3</sub>, A<sub>1</sub>, and A<sub>2A</sub> receptors. *K<sub>i</sub>* values are summarized in Tables 2, 3, 4, and 5.

**Effects of Amide Group at C-2 Position and Pyridine Ring at C-5 Position** First, the effect of the substituent on the 2-position (R<sup>2</sup>) of thiazole ring was evaluated with **6a**, **12** and **7a**, as shown in Table 2. Although the acetamide **7a** showed strong affinity to hA<sub>3</sub>AR, removal of the acetyl group or replacement with a methyl group led to weak affinity (**7a** vs. **6a** and **12**). Introduction of a methyl group into the 2-acetamide **7a** also reduced affinity (**7a** vs. **7e**). These results suggested that the carbonyl group and hydrogen atom of amide at the C-2 position were important to interact with the receptor. The structure-activity relationships (SAR) around the pyridine ring at the C-5 position of the thiazole nucleus were evaluated with **7a**–**d**. The 2-pyridyl derivative **7c** and 5-unsubstituted derivative **7d** were less active than 4- or 3-pyridyl derivatives **7a** and **7b**, indicating that nitrogen atoms of 3- and 4-pyridyl groups are important for hA<sub>3</sub>AR affinity. The role of these substituents will be discussed in the Molecular Modeling Section.

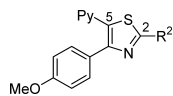
The rA<sub>3</sub>AR affinity of the 3-pyridyl derivative **7b**, 5-unsubstituted compound **7d** and *N*-methylacetamide compound **7e** was examined; however, these compounds showed less affinity than the lead compound **7a**.

**SAR of the Substituent on Benzene Ring at C-4 Position of 1,3-Thiazole** Because of fairly good rA<sub>3</sub>AR affinity, we selected the 4-pyridyl group at C-5 position of the thiazole ring, and the influence of substituents on the phenyl ring at C-4 position of thiazole was investigated, as shown in

Table 1. Physicochemical Properties of 5-Pyridyl-1,3-thiazole Derivatives



Compd.	Py	R <sup>1</sup>	R <sup>2</sup>	Formula	mp (°C)	Anal.
6a	4-Py	4-MeO	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS	282—284	C, H, N
6b	3-Py	4-MeO	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS	265—266	C, H, N
6c	2-Py	4-MeO	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS	217—218	C, H, N
6d	H	4-MeO	NH <sub>2</sub>	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> OS	203—204	C, H, N
6e	4-Py	4-MeO	NHMe	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> OS · 0.5H <sub>2</sub> O	175—177	C, H, N
6f	4-Py	3-MeO	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS	232—234	C, H, N
6g	4-Py	2-MeO	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS · 0.2H <sub>2</sub> O	213—215	C, H, N
6h	4-Py	4-Me	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> S	296—298	C, H, N
6i	4-Py	3-Me	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> S	255—258	C, H, N
6j	4-Py	2-Me	NH <sub>2</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> S · 0.2H <sub>2</sub> O	235—238	C, H, N
6k	4-Py	4-Cl	NH <sub>2</sub>	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> S	>300	C, H, N
6l	4-Py	3-Cl	NH <sub>2</sub>	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> S	256—258	C, H, N
6m	4-Py	2-Cl	NH <sub>2</sub>	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> S	232—235	C, H, N
6n	4-Py	4-Et	NH <sub>2</sub>	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> S	285—288	C, H, N
6o	4-Py	4- <sup>n</sup> Pr	NH <sub>2</sub>	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> S	240—242	C, H, N
6p	4-Py	4- <sup>n</sup> Bu	NH <sub>2</sub>	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> S · 0.5H <sub>2</sub> O	204—206	C, H, N
6q	4-Py	4- <sup>i</sup> Pr	NH <sub>2</sub>	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> S	267—269	C, H, N
6r	4-Py	4- <sup>t</sup> Bu	NH <sub>2</sub>	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> S · 0.5H <sub>2</sub> O	254—257	C, H, N
6s	4-Py	4-Me <sub>2</sub> N	NH <sub>2</sub>	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub> S	309—311	C, H, N
6t	4-Py	3,4-diMe	NH <sub>2</sub>	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> S	248—250	C, H, N
6u	4-Py	3,5-diMe	NH <sub>2</sub>	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> S	242—244	C, H, N
6v	4-Py	3,4-di(MeO)	NH <sub>2</sub>	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	218—219	C, H, N
6w	4-Py	3,4-(OCH <sub>2</sub> O)	NH <sub>2</sub>	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	273—275	C, H, N
6x	3-Py	4- <sup>t</sup> Bu	NH <sub>2</sub>	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> S	239—241	C, H, N
6y	3-Py	3,5-diMe	NH <sub>2</sub>	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> S	237—240	C, H, N
6z	4-Py	4-HO	NH <sub>2</sub>	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S · 3H <sub>2</sub> O	323—326	C, H, N
6aa	4-Py	4-MeO	CH <sub>2</sub> CO <sub>2</sub> Et	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S	Oil	
7a	4-Py	4-MeO	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	282—284	C, H, N
7b	3-Py	4-MeO	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	119—120	C, H, N
7c	2-Py	4-MeO	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	230—232	C, H, N
7d	H	4-MeO	NHAc	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S	192—193	C, H, N
7e	4-Py	4-MeO	NMeAc	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	180—181	C, H, N
7f	4-Py	3-MeO	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S · 0.3H <sub>2</sub> O	234—236	C, H, N
7g	4-Py	2-MeO	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	259—261	C, H, N
7h	4-Py	4-Me	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	308—309	C, H, N
7i	4-Py	3-Me	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	287—289	C, H, N
7j	4-Py	2-Me	NHAc	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	272—274	C, H, N
7k	4-Py	4-Cl	NHAc	C <sub>16</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub> S · 0.2H <sub>2</sub> O	317—320	C, H, N
7l	4-Py	3-Cl	NHAc	C <sub>16</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub> S	290—293	C, H, N
7m	4-Py	2-Cl	NHAc	C <sub>16</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub> S	292—293	C, H, N
7n	4-Py	4-Et	NHAc	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S · 0.1H <sub>2</sub> O	294—295	C, H, N
7o	4-Py	4- <sup>n</sup> Pr	NHAc	C <sub>19</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S · 0.2H <sub>2</sub> O	256—258	C, H, N
7p	4-Py	4- <sup>n</sup> Bu	NHAc	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> S	259—261	C, H, N
7q	4-Py	4- <sup>i</sup> Pr	NHAc	C <sub>19</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S	295—297	C, H, N
7r	4-Py	4- <sup>t</sup> Bu	NHAc	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> S	280—281	C, H, N
7s	4-Py	4-Me <sub>2</sub> N	NHAc	C <sub>18</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S · 0.2H <sub>2</sub> O	289—291	C, H, N
7t	4-Py	3,4-diMe	NHAc	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	248—250	C, H, N
7u	4-Py	3,5-diMe	NHAc	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S · 0.1H <sub>2</sub> O	284—286	C, H, N
7v	4-Py	3,4-di(MeO)	NHAc	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S	265—267	C, H, N
7w	4-Py	3,4-(OCH <sub>2</sub> O)	NHAc	C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S	295—296	C, H, N
7x	4-Py	4- <sup>t</sup> Bu	NHCOEt	C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> S	295—297	C, H, N
7y	4-Py	4- <sup>t</sup> Bu	NHCO( <sup>n</sup> Pen)	C <sub>24</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub> S	309—311	C, H, N
7z	4-Py	4- <sup>t</sup> Bu	NHCOPh	C <sub>25</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> S	292—294	C, H, N
7aa	4-Py	4- <sup>t</sup> Bu	NHCO(3-Py)	C <sub>24</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> S	326—328	C, H, N
7ab	4-Py	4- <sup>t</sup> Bu	NHCO(4-Py)	C <sub>24</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> S	326—329	C, H, N
7ac	4-Py	3,5-diMe	NHCOEt	C <sub>19</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S	291—293	C, H, N
7ad	4-Py	3,5-diMe	NHCO( <sup>n</sup> Pen)	C <sub>22</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> S	275—278	C, H, N
7ae	4-Py	3,5-diMe	NHCOPh	C <sub>23</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S	285—286	C, H, N
7af	4-Py	3,5-diMe	NHCO(3-Py)	C <sub>22</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S	267—270	C, H, N
7ag	4-Py	3,5-diMe	NHCO(4-Py)	C <sub>22</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S · 0.2H <sub>2</sub> O	302—304	C, H, N
7ah	3-Py	4- <sup>t</sup> Bu	NHAc	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> S · 0.3H <sub>2</sub> O	228—230	C, H, N
7ai	3-Py	4- <sup>t</sup> Bu	NHCO(3-Py)	C <sub>24</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> S	251—253	C, H, N
7aj	3-Py	3,5-diMe	NHAc	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	288—289	C, H, N
7ak	3-Py	3,5-diMe	NHCO(3-Py)	C <sub>22</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S	277—278	C, H, N
9	4-Py	4-AcO	NHAc	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> S · 0.2H <sub>2</sub> O	254—257	C, H, N
10	4-Py	4-HO	NHAc	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S · 0.7H <sub>2</sub> O	285—287	C, H, N
11a	4-Py	4-EtO	NHAc	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	206—209	C, H, N
11b	4-Py	4- <sup>n</sup> BuO	NHAc	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> S	201—203	C, H, N
12	4-Py	4-MeO	Me	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> S · 0.1H <sub>2</sub> O	132—133	C, H, N

Table 2. Binding Affinity for Human A<sub>3</sub>, A<sub>1</sub> and A<sub>2A</sub>, and Rat A<sub>3</sub> Receptors

Compd.	Py	R <sup>2</sup>	K <sub>i</sub> (nM)			
			hA <sub>3</sub>	hA <sub>1</sub>	hA <sub>2A</sub>	rA <sub>3</sub>
<b>6a</b>	4-Py	NH <sub>2</sub>	>285	NT <sup>a)</sup>	NT <sup>a)</sup>	NT <sup>a)</sup>
<b>12</b>	4-Py	Me	>285	>666	>826	NT <sup>a)</sup>
<b>7a</b>	4-Py	NHAc	0.16	>666	200	23
<b>7b</b>	3-Py	NHAc	0.08	>666	145	160
<b>7c</b>	2-Py	NHAc	9.0	>666	160	NT <sup>a)</sup>
<b>7d<sup>b)</sup></b>	(H)	NHAc	5.8	>666	>826	>980
<b>7e</b>	4-Py	NMeAc	7.9	>666	>826	360

a) NT indicates 'not tested'. b) **7d** is 5-unsubstituted derivative.

Table 3.

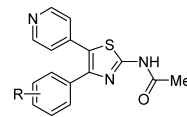
Introduction of methoxy (**7a, f**), methyl (**7h, i**) and chloro (**7k, l**) substituents into 4- and 3-positions of the phenyl ring showed potent activity for hA<sub>3</sub>AR, and substitution (**7a, h, k**) at 4-position of the phenyl ring was more favored for rA<sub>3</sub>AR than corresponding substitution (**7f, i, l**) at 3-position. The introduction of substituents (**7g, j, m**) into the 2-position of the phenyl ring led to significant reduction of hA<sub>3</sub>AR activity. As for receptor sub-type selectivity, methyl (**7h—j**) and chloro (**7k—m**) derivatives exhibited somewhat potent activity for hA<sub>1</sub>AR and hA<sub>2A</sub>AR. In general, the 2- (**7g, j, m**) or 3-substituted (**7f, i, l**) compounds showed less hA<sub>3</sub>AR selectivity than the corresponding 4-substituted compounds (**7a, f, g**).

Therefore, we focused the substituent at 4-position on the benzene ring, and examined further to identify the effect of activity and selectivity. Introduction of the bulky substituent at 4-position slightly diminished hA<sub>3</sub>AR affinity but increased hA<sub>3</sub>AR selectivity and rA<sub>3</sub>AR affinity. The 4-ethyl **7n** and 4-propyl **7o** derivatives gave slightly less hA<sub>3</sub>AR and rA<sub>3</sub>AR affinity than 4-methyl **7h**, whereas the hA<sub>3</sub>AR selectivity of these compounds increased. Although compounds **7p** and **7q** showed good hA<sub>3</sub>AR affinity and poor rA<sub>3</sub>AR affinity, the 4-*tert*-butyl derivative **7r** showed potent rA<sub>3</sub>AR affinity as 4-methyl derivative **7h**. Although alkoxy derivatives **11a** and **11b** were synthesized and tested for their affinity, these compounds showed less affinity for hA<sub>3</sub>AR than methoxy derivative **7a**. The 4-dimethylamino derivative **7s** showed good hA<sub>3</sub>AR affinity and selectivity. These results suggested that the steric effect of the substituent would be a more important factor than the electronic effect for hA<sub>3</sub>AR selectivity and rA<sub>3</sub>AR affinity.

As for disubstituted derivatives, 3,4-dimethyl **7t** and 3,4-methylenedioxy derivatives **7w** showed good hA<sub>3</sub>AR affinity, but the selectivity was insufficient. Dimethoxy **7v** and 3,4-methylenedioxy compounds **7w** gave potent hA<sub>3</sub>AR affinity as well as good selectivity, but showed moderate rA<sub>3</sub>AR affinity. Among these disubstituted derivatives, the 3,5-dimethyl derivative **7u** showed potent human and rat A<sub>3</sub>AR affinity as well as good selectivity.

On the basis of these results, we chose 4-*tert*-butyl and 3,5-dimethyl groups as representative substituents on the benzene ring for the next SAR study around 2-position of the thiazole.

Table 3. Effect of Substituent on 4-Phenyl Ring



Compd.	R	K <sub>i</sub> (nM)			
		hA <sub>3</sub>	hA <sub>1</sub>	hA <sub>2A</sub>	rA <sub>3</sub>
<b>7a</b>	4-MeO	0.16	>666	200	23
<b>7f</b>	3-MeO	0.12	110	61	69
<b>7g</b>	2-MeO	1.1	46	350	1100
<b>7h</b>	4-Me	0.08	9.3	27	32
<b>7i</b>	3-Me	0.15	25	29	140
<b>7j</b>	2-Me	1.8	62	460	>1000
<b>7k</b>	4-Cl	0.10	20	56	480
<b>7l</b>	3-Cl	0.15	17	18	>1000
<b>7m</b>	2-Cl	0.73	59	110	2100
<b>7n</b>	4-Et	0.20	70	130	81
<b>7o</b>	4- <sup>n</sup> Pr	0.28	180	>826	64
<b>7p</b>	4- <sup>n</sup> Bu	0.26	>666	>826	56
<b>7q</b>	4- <sup>i</sup> Pr	0.40	>666	>826	180
<b>7r</b>	4- <sup>t</sup> Bu	0.21	>666	>826	45
<b>11a</b>	4-EtO	22	170	>826	>980
<b>11b</b>	4- <sup>n</sup> BuO	130	>666	>826	230
<b>7s</b>	4-Me <sub>2</sub> N	0.26	>666	>826	49
<b>7t</b>	3,4-diMe	0.20	34	49	9.7
<b>7u</b>	3,5-diMe	0.25	>666	>826	4.1
<b>7v</b>	3,4-di(MeO)	0.30	>666	>826	93
<b>7w</b>	3,4-(OCH <sub>2</sub> O)	0.29	19	25	33

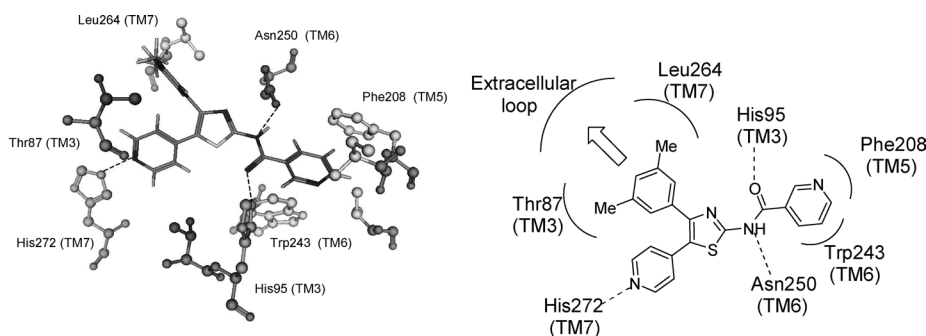
**SAR of Acyl Group at 2-Position on 1,3-Thiazole** The influence of substituents at 2-position of thiazole was evaluated, as shown in Table 4. Among 4-*tert*-butyl derivatives, it was observed that propionyl **7x** and isonicotinoyl **7ab** retained activity, and cyclopentylcarbonyl **7y**, benzoyl **7z** and nicotinoyl **7aa** slightly reduced hA<sub>3</sub>AR affinity. 3,5-Dimethylphenyl derivatives **7ac—ag** showed comparable hA<sub>3</sub>AR activity to acetyl compound **7u**. For rA<sub>3</sub>AR affinity, introduction of an aromatic acyl substituent such as benzoyl **7z**, **7ae**, nicotinoyl **7aa**, **7af**, or isonicotinoyl **7ag** led to a dramatic increase in rA<sub>3</sub>AR affinity. Among these compounds, benzoyl derivative **7ae** and nicotinoyl derivatives **7aa**, **7af** showed the best results for receptor binding activity for both hA<sub>3</sub>AR and rA<sub>3</sub>AR as well as selectivity over hA<sub>1</sub>AR and hA<sub>2A</sub>AR.

Finally, we investigated the adenosine receptor affinity of compounds which have 3-pyridyl at 5-position on 1,3-thiazole, as shown in Table 4, because 3-pyridyl derivative **7b** (hA<sub>3</sub>; K<sub>i</sub>=0.08 nM) was stronger than the relative 4-pyridyl derivative **7a** (hA<sub>3</sub>; K<sub>i</sub>=0.16 nM). Among 4-*tert*-butylphenyl derivatives, replacement of 4-pyridyl with 3-pyridyl led to the reduction of both hA<sub>3</sub>AR and rA<sub>3</sub>AR affinity (**7r** vs. **7ah**, and **7u** vs. **7aj**). In 3,5-dimethylphenyl derivatives, 2-acetamide **7aj** showed strong hA<sub>3</sub>AR activity; however, its rA<sub>3</sub>AR activity was weak. Although 2-nicotinoyl derivative **7ak** showed stronger rA<sub>3</sub>AR affinity than **7aj**, its affinity for both A<sub>3</sub>AR was less than that of the corresponding 4-pyridyl derivative **7af**.

**Molecular Modeling Study** To explain the above SAR, we tried to perform a docking study using a homology model of the hA<sub>3</sub>AR constructed from the crystal structure of bovine rhodopsin (PDBID: 1F88) as a template, based on

Table 4. Effect of Acyl Group at 2-Position on Thiazole

Compd.	Py	R <sup>1</sup>	R <sup>2</sup>	K <sub>i</sub> (nM)			
				hA <sub>3</sub>	hA <sub>1</sub>	hA <sub>2A</sub>	rA <sub>3</sub>
<b>7r</b>	4-Py	4- <i>t</i> Bu	NHCOMe	0.21	>666	>826	45
<b>7x</b>	4-Py	4- <i>t</i> Bu	NHCOEt	0.32	>666	>826	30
<b>7y</b>	4-Py	4- <i>t</i> Bu	NHCO( <i>t</i> Pen)	0.88	>666	>826	11
<b>7z</b>	4-Py	4- <i>t</i> Bu	NHCOPh	1.0	>666	>826	2.5
<b>7aa</b>	4-Py	4- <i>t</i> Bu	NHCO(3-Py)	0.50	>666	>826	4.3
<b>7ab</b>	4-Py	4- <i>t</i> Bu	NHCO(4-Py)	0.35	>666	>826	130
<b>7ah</b>	3-Py	4- <i>t</i> Bu	NHCOMe	7.7	>666	>826	>1000
<b>7ai</b>	3-Py	4- <i>t</i> Bu	NHCO(3-Py)	19	>666	>826	550
<b>7u</b>	4-Py	3,5-diMe	NHCOMe	0.25	>666	>826	4.1
<b>7ac</b>	4-Py	3,5-diMe	NHCOEt	0.24	>666	>826	7.0
<b>7ad</b>	4-Py	3,5-diMe	NHCO( <i>t</i> Pen)	0.24	>666	76	3.5
<b>7ae</b>	4-Py	3,5-diMe	NHCOPh	0.42	>666	>826	1.2
<b>7af</b>	4-Py	3,5-diMe	NHCO(3-Py)	0.36	>666	>826	1.6
<b>7ag</b>	4-Py	3,5-diMe	NHCO(4-Py)	0.34	>666	>826	4.0
<b>7aj</b>	3-Py	3,5-diMe	NHCOMe	0.50	>666	63	>1000
<b>7ak</b>	3-Py	3,5-diMe	NHCO(3-Py)	2.1	>666	>826	120

Fig. 2. Schematic Model for Binding hA<sub>3</sub>AR with Compound **7af**

mutational studies, as previously reported.<sup>33,34</sup> The homology model of hA<sub>3</sub>AR was constructed using the molecular operating environment (MOE 2005.06, Chemical Computing Group: Montreal, Canada), and docking was performed manually using GOLD v3.0.<sup>35</sup> Figure 2 shows the most reasonable binding mode between A<sub>3</sub>AR and compound **7af**.

In this model, the amide moiety at 2-position of thiazole in **7af** interacted with Asn250 (TM6) and His95 (TM3), suggesting that the amine **6a** and methyl derivative **12** without an acyl group showed weak hA<sub>3</sub>AR binding activity. The pyridyl group at 2-position of **7af** was placed in the hydrophobic pocket bordered by Phe208 (TM5) and Trp243 (TM6), and it was predicted that no residue of hA<sub>3</sub>AR would interact with the nitrogen atom of the pyridyl group. The replacement of Phe208 with Leu in rA<sub>3</sub>AR and  $\pi$ - $\pi$  interaction between Trp243 and the aryl substituent of 2 position of thiazole could explain the increased affinity of rA<sub>3</sub>AR. The third hydrogen bond between the nitrogen atom of the pyridine ring and His272 (TM7) was predicted and the 4-position of the phenyl ring of **7af** was surrounded by Leu264 (TM7) and Thr87 (TM3). This result also suggested that 2-pyridyl compound **7c** and hydrogen compound **7d** showed less activ-

ity than 3-pyridyl compound **7b** and 4-pyridyl compound **7a**. Although this model can explain some SAR of these compounds for hA<sub>3</sub>AR, it was difficult to explain the SAR of the substituent at 4-position on the phenyl ring from the results of our study. In this model, the substituent of the 4-position of thiazole was directed toward the extracellular loop and subtype selectivity of the compound might be explained by interaction with the loop. In general, extracellular loops are so flexible that modeling studies of these areas are very difficult. As a species difference, Leu264 (TM7) replaced Ser and Thr87 (TM3) replaced Met in rA<sub>3</sub>AR, with the model suggesting that the space for the ligand binding site in rA<sub>3</sub>AR was wider than hA<sub>3</sub>AR. Better accommodation might be one reason that 3,5-dimethyl and 4-*tert*-butyl phenyl moieties showed good rA<sub>3</sub>AR affinity.

**In Vivo Efficacy of Selected A<sub>3</sub>AR Antagonists** On the basis of the adenosine receptor binding assay, the six compounds listed were selected and evaluated for inhibition activity on IB-MECA (*N*<sup>6</sup>-(3-iodobenzyl)-9-[5-(methylcarbamoyl)- $\beta$ -D-ribofuranosyl]adenine)-induced plasma protein extravasation in the skin of rats, as shown in Table 5. Although compounds **7z** and **ae** showed no significant activity

in this model at a dose of 10 mg/kg, *p.o.*, the other four compounds **7u**, **7aa**, **7af** and **7ag** showed significant inhibitory activity in this model. Compounds **7u** and **7af**, in particular completely inhibited dye leakage at 10 mg/kg, *p.o.* and PK data of compounds **7u** and **7af** in rats is shown in Table 5. Compound **7af** demonstrated a good oral absorption profile and bioavailability (62.5±19.0%), whereas compound **7u** showed a poor oral absorption profile and low bioavailability

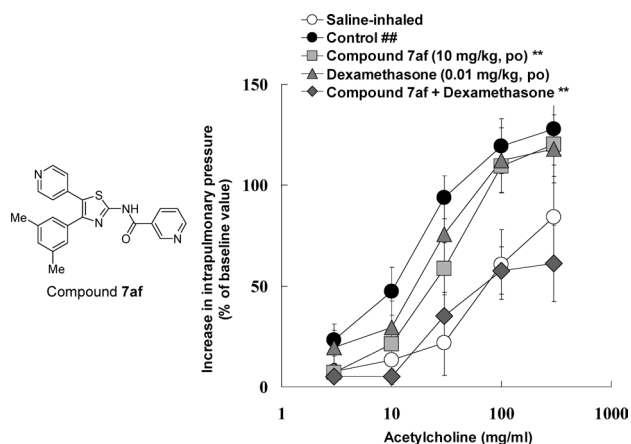


Fig. 3. Effect of Combined Administration of **7af** and Dexamethasone on Antigen-Induced Airway Hyper-Responsiveness to Acetylcholine in Actively Sensitized BN Rats

BN rats were actively sensitized and 3 weeks later were challenged with saline or 1% OVA. Airway responsiveness to acetylcholine was measured 23–30 h after antigen challenge. Compound **7af** (10 mg/kg) and dexamethasone (0.01 mg/kg) were orally administered 1 h before and 7 h after antigen challenge. Data are the mean±S.E. of 8 rats. #  $p < 0.01$ , vs. saline-inhaled group, \*\*  $p < 0.01$ , vs. OVA-inhaled control group (two-way ANOVA).

(9.9%).

To determine the potency of  $A_3AR$  antagonist as an anti-asthmatic drug, the selected compound **7af** was evaluated in an antigen-induced asthma model using Brown Norway (BN) rats. Compound **7af** dose-dependently inhibited antigen-induced hyper-responsiveness to acetylcholine in actively sensitized BN rats and this effect was statistically significant at oral administration of 10 mg/kg (Fig. 3). Compound **7af** increased the anti-asthmatic effect of dexamethasone by combination therapy and these results suggested that the  $A_3AR$  antagonist could become a new type of anti-asthma drug as an enhancer of steroids.

## Conclusion

In this study, we found a novel series of 4-phenyl-5-pyridyl-1,3-thiazole derivatives with human  $A_3AR$  affinity, which had received considerable attention for their structural similarity to p38 MAPK inhibitors.<sup>30,31</sup> The SAR of these compounds was summarized as 1) pyridyl moiety at 5-position of thiazole is important for affinity of  $hA_3AR$  and  $rA_3AR$ ; 2) the substituent on the phenyl ring at 4-position of thiazole is related to adenosine receptor subtype selectivity; 3) the acyl moiety at 2-position of thiazole is important for affinity of  $rA_3AR$ , as shown in Fig. 4. As a result of the SAR study, the highly potent  $hA_3AR$  and  $rA_3AR$  antagonist **7af** has been identified. This compound inhibited IB-MECA-induced plasma protein extravasation in the skin of rats, and showed good oral absorption in rats. Compound **7af** significantly inhibited antigen-induced hyper-responsiveness to acetylcholine in actively sensitized BN rats. These results show that 4-phenyl-5-pyridyl-1,3-thiazole derivatives are po-

Table 5. Inhibition Activity on IB-MECA Induced Plasma Protein Extravasation in the Skin of Rats and Plasma Concentration after Oral Administration in Rats

Compd.	R <sup>1</sup>	R <sup>2</sup>	K <sub>i</sub> (nm)		IB-NECA rat (%inh.) Dose (mg/kg, <i>p.o.</i> )		rat PK <sup>a)</sup> Dose (10 mg/kg, <i>p.o.</i> )		
			$hA_3AR$	$rA_3AR$	1	10	C <sub>max</sub> (μg/ml)	AUC <sub>0–24h</sub> (μg·h/ml)	BA (%)
<b>7u</b>	3,5-Me <sub>2</sub>	NHCOMe	0.25	4.1	73**	107**	0.035±0.011	0.263±0.053	9.9±2.0
<b>7z</b>	4-'Bu	NHCOPh	1.0	2.5	41	78	NT <sup>b)</sup>	NT <sup>b)</sup>	NT <sup>b)</sup>
<b>7aa</b>	4-'Bu	NHCO(3-Py)	0.50	4.3	43**	91**	NT <sup>b)</sup>	NT <sup>b)</sup>	NT <sup>b)</sup>
<b>7ae</b>	3,5-Me <sub>2</sub>	NHCOPh	0.42	1.2	48	77	NT <sup>b)</sup>	NT <sup>b)</sup>	NT <sup>b)</sup>
<b>7af</b>	3,5-Me <sub>2</sub>	NHCO(3-Py)	0.36	1.6	83**	102**	0.871±0.268	4.273±1.302	62.5±19.0
<b>7ag</b>	3,5-Me <sub>2</sub>	NHCO(4-Py)	0.34	4.0	77**	80**	NT <sup>b)</sup>	NT <sup>b)</sup>	

\*\*  $p < 0.01$  vs. IB-MECA injection control (Dunnett's test).  $n = 6$ . *a)*  $n = 3$ . *b)* NT indicates 'not tested'.

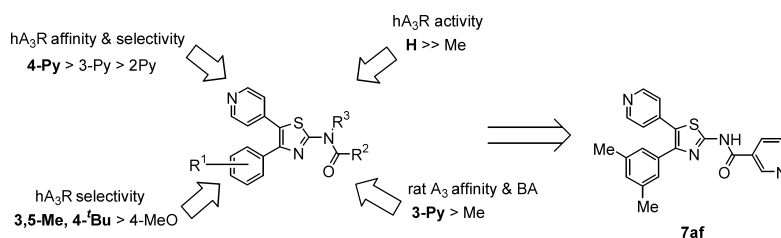


Fig. 4. Structural Factors of Thiazole Compounds Affected the Binding Profile

tential candidates to evaluate A<sub>3</sub>AR antagonists as new drugs for the treatment of inflammatory diseases, such as asthma.

### Experimental

**General** Melting points (mp) were determined on a Yanagimoto micro melting point apparatus or Büche B-545 and are uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer, with tetramethylsilane as the internal standard. TLC analyses were carried out on Merck Kieselgel 60 F<sub>254</sub> plates. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd., and are within ±0.4% of the theoretical values unless otherwise noted. THF was distilled over calcium hydride prior to use and other solvents and reagents were used without purification. Extracted solutions were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> unless otherwise noted and the concentration of the organic solution was carried out under reduced pressure. Chromatographic purification was carried out on silica gel columns (Kieselgel 60, 0.063–0.22 mm, Merck) unless otherwise noted. The yields reported are not optimized.

The 1-benzoyl-2-methylaziridines **2a–i**, 1-phenyl-2-pyridylethanones **4a–k** and **4p**, 2-bromo-1-phenyl-2-pyridylethanones **5a–k** and **5p**, 4-phenyl-5-pyridyl-1,3-thiazol-2-ylamines **6a–c**, **6f–m**, and **6r**, and *N*-(4-phenyl-5-pyridyl-1,3-thiazol-2-yl)acetamides **7a–c**, **7f–m** and **7r** were prepared according to a previous report.<sup>30</sup>

The 1-benzoylaziridine derivatives **2** were unstable under silica gel column chromatography or distillation, so these compounds were used for next reaction without purification as following typical condition.

**1-(4-Ethylbenzoyl)-2-methylaziridine (2j)** A solution of 2-methylaziridine (14.3 ml, 0.183 mol) in diethyl ether (170 ml) was added to 2 N aqueous sodium hydroxide solution (95 ml). This mixture was cooled to 0 °C and 4-ethylbenzoyl chloride (28.0 g, 0.166 mol) was added dropwise to the mixture. After the addition, the mixture was further stirred for 1 h at 0 °C. The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was dried, and concentrated to afford 36.4 g (yield quant.) of **2j** as an oil, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.27 (3H, t, *J*=7.6 Hz), 1.39 (3H, d, *J*=5.5 Hz), 2.12 (1H, d, *J*=2.9 Hz), 2.50–2.61 (2H, m), 2.71 (2H, q, *J*=7.6 Hz), 7.47 (2H, d, *J*=8.8 Hz), 7.96 (2H, d, *J*=8.8 Hz).

**1-(4-Propylbenzoyl)-2-methylaziridine (2k)** This compound was prepared from 4-propylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.96 (3H, t, *J*=7.3 Hz), 1.39 (3H, d, *J*=5.5 Hz), 1.57–1.75 (2H, m), 2.12 (1H, d, *J*=3.3 Hz), 2.50–2.59 (2H, m), 2.65 (2H, t, *J*=7.7 Hz), 7.26 (2H, d, *J*=8.1 Hz), 7.94 (2H, d, *J*=8.1 Hz).

**1-(4-Butylbenzoyl)-2-methylaziridine (2l)** This compound was prepared from 4-butylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.94 (3H, t, *J*=7.1 Hz), 1.26–1.47 (5H, m), 1.54–1.73 (2H, m), 2.12 (1H, d, *J*=2.9 Hz), 2.51–2.62 (2H, m), 2.67 (2H, t, *J*=7.7 Hz), 7.26 (2H, d, *J*=8.1 Hz), 7.94 (2H, d, *J*=8.1 Hz).

**1-[4-(1-Methylethyl)benzoyl]-2-methylaziridine (2m)** This compound was prepared from 4-(1-methylethyl)benzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.28 (6H, d, *J*=7.0 Hz), 1.40 (3H, d, *J*=5.4 Hz), 2.12 (1H, d, *J*=3.2 Hz), 2.51–2.63 (2H, m), 2.87–3.03 (1H, m), 7.31 (2H, d, *J*=8.4 Hz), 7.96 (2H, d, *J*=8.4 Hz).

**1-(3,4-Dimethylbenzoyl)-2-methylaziridine (2o)** This compound was prepared from 3,4-dimethylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.39 (3H, d, *J*=5.5 Hz), 2.12 (1H, d, *J*=3.3 Hz), 2.32 (6H, s), 2.49–2.61 (2H, m), 7.21 (1H, d, *J*=7.7 Hz), 7.77 (1H, dd, *J*=7.7, 1.8 Hz), 7.80 (1H, d, *J*=1.8 Hz).

**1-(3,5-Dimethylbenzoyl)-2-methylaziridine (2p)** This compound was prepared from 3,5-dimethylbenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.39 (3H, d, *J*=5.5 Hz), 2.13 (1H, d, *J*=3.7 Hz), 2.37 (6H, s), 2.47–2.62 (2H, m), 7.19 (1H, s), 7.64 (2H, s).

**1-(3,4-Dimethoxybenzoyl)-2-methylaziridine (2q)** This compound was prepared from 3,4-dimethoxybenzoyl chloride as described in the synthesis of **2j**, as an oil, yield quant., <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (3H, d, *J*=5.5 Hz), 2.12 (1H, d, *J*=3.3 Hz), 2.51–2.63 (2H, m), 3.94 (3H, s), 3.95 (3H, s), 6.92 (1H, d, *J*=8.5 Hz), 7.56 (1H, d, *J*=2.2 Hz), 7.69 (1H, dd, *J*=8.5, 2.2 Hz).

**1-(1,3-Benzodioxol-5-ylcarbonyl)-2-methylaziridine (2r)** This compound was prepared from 1,3-benzodioxol-5-ylcarbonyl chloride as described in the synthesis of **2j**, as an oil, yield 92%, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.38 (3H, d, *J*=4.9 Hz), 2.11 (1H, d, *J*=3.1 Hz), 2.48–2.64 (2H, m), 6.05 (2H, s), 6.86 (1H, d, *J*=8.2 Hz), 7.48 (1H, d, *J*=1.7 Hz), 7.65 (1H, dd, *J*=8.2, 1.7 Hz).

**1-(4-Ethylphenyl)-2-(4-pyridyl)ethanone (4l)** Under argon atmosphere, a solution of diisopropylamine (15.4 ml) in tetrahydrofuran (100 ml)

was cooled to –78 °C and a solution of 1.6 M *n*-butyllithium in hexane (68.3 ml) was added dropwise to the solution. After addition, the solution was stirred for 10 min and a solution of 4-methylpyridine (**3a**) (9.31 g) in tetrahydrofuran (10 ml) was added dropwise to the LDA solution. The reaction mixture was allowed to warm up to –10 °C and stirred for 20 min. The resulting mixture was cooled to –78 °C and a solution of **2j** (18.9 g) in tetrahydrofuran (10 ml) was added dropwise to the mixture. After addition, the mixture was stirred for 1 h at –78 °C and then the reaction mixture was allowed to warm to room temperature. Water (300 ml) was added to the mixture and the organic phase was separated. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried and concentrated to give crude crystals, which were recrystallized from ethyl acetate–isopropyl ether to afford 9.78 g (yield 43%) of **4l** as a solid, mp 87–89 °C (ethyl acetate–isopropyl ether), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.26 (3H, t, *J*=7.5 Hz), 2.72 (2H, q, *J*=7.5 Hz), 4.27 (2H, s), 7.21 (2H, d, *J*=6.2 Hz), 7.31 (2H, d, *J*=8.4 Hz), 7.93 (2H, d, *J*=8.4 Hz), 8.56 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.83; H, 6.72; N, 6.20.

**1-(4-Propylphenyl)-2-(4-pyridyl)ethanone (4m)** This compound was prepared from **2k** as described in the synthesis of **4l** as a solid, yield 32%, mp 71–72 °C (ethyl acetate–hexane), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.95 (3H, t, *J*=7.3 Hz), 1.57–1.76 (2H, m), 2.66 (2H, t, *J*=7.7 Hz), 4.27 (2H, s), 7.21 (2H, d, *J*=6.2 Hz), 7.29 (2H, d, *J*=8.6 Hz), 7.92 (2H, d, *J*=8.6 Hz), 8.56 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>16</sub>H<sub>17</sub>NO: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.33; H, 7.16; N, 5.79.

**1-(4-Butylphenyl)-2-(4-pyridyl)ethanone (4n)** This compound was prepared from **2l** as described in the synthesis of **4l** as a solid, yield 20%, mp 41–43 °C (isopropyl ether–hexane), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.93 (3H, t, *J*=7.1 Hz), 1.26–1.47 (2H, m), 1.54–1.72 (2H, m), 2.68 (2H, t, *J*=7.7 Hz), 4.27 (2H, s), 7.21 (2H, d, *J*=6.0 Hz), 7.29 (2H, d, *J*=8.6 Hz), 7.92 (2H, d, *J*=8.6 Hz), 8.56 (2H, d, *J*=6.0 Hz). *Anal.* Calcd for C<sub>17</sub>H<sub>19</sub>NO: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.55; H, 7.31; N, 5.47.

**1-[4-(1-Methylethyl)phenyl]-2-(4-pyridyl)ethanone (4o)** This compound was prepared from **2m** as described in the synthesis of **4l** as a solid, yield 43%, mp 86–88 °C (isopropyl ether–hexane), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.27 (6H, d, *J*=7.0 Hz), 2.87–3.06 (1H, m), 4.27 (2H, s), 7.21 (2H, d, *J*=6.2 Hz), 7.34 (2H, d, *J*=8.4 Hz), 7.94 (2H, d, *J*=8.4 Hz), 8.56 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>16</sub>H<sub>17</sub>NO: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.29; H, 7.18; N, 5.84.

**1-[4-(*N,N*-Dimethylamino)phenyl]-2-(4-pyridyl)ethanone (4q)** Under argon atmosphere, a solution of diisopropylamine (15.4 ml) in tetrahydrofuran (100 ml) was cooled to –78 °C and a solution of 1.6 M *n*-butyllithium in hexane (68.3 ml) was added dropwise to the solution. After addition, the solution was stirred for 10 min and a solution of 4-methylpyridine (**3a**) (9.31 g) in tetrahydrofuran (10 ml) was added dropwise to the LDA solution. The reaction mixture was allowed to warm up to –10 °C and stirred for 1 h. A solution of ethyl 4-(*N,N*-dimethylamino)benzoate (21.3 g) in tetrahydrofuran (10 ml) was added dropwise to the mixture. After addition, the mixture was stirred for 1 h at –10 °C and then the reaction mixture was allowed to warm to room temperature. Water (100 ml) was added to the mixture and the organic phase was separated. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed, dried and concentrated to give crude crystals, which were recrystallized from ether to afford 7.19 g (yield 30%) of **4q** as a solid, mp 189–192 °C, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.07 (6H, s), 4.19 (2H, s), 6.66 (2H, d, *J*=9.0 Hz), 7.22 (2H, d, *J*=5.9 Hz), 7.90 (2H, d, *J*=9.0 Hz), 8.53 (2H, d, *J*=5.9 Hz). *Anal.* Calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.98; H, 6.78; N, 11.65.

**1-(3,4-Dimethylphenyl)-2-(4-pyridyl)ethanone (4r)** This compound was prepared from **2o** as described in the synthesis of **4l** as a solid, yield 40%, mp 81–83 °C (ethyl acetate–isopropyl ether), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.33 (6H, s), 4.26 (2H, s), 7.21 (2H, d, *J*=5.9 Hz), 7.24 (1H, d, *J*=7.9 Hz), 7.73 (1H, dd, *J*=7.9, 1.8 Hz), 7.77 (1H, d, *J*=1.8 Hz), 8.56 (2H, d, *J*=5.9 Hz). *Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.89; H, 6.72; N, 6.15.

**1-(3,5-Dimethylphenyl)-2-(4-pyridyl)ethanone (4s)** This compound was prepared from **2p** as described in the synthesis of **4l** as a solid, yield 58%, mp 90–91 °C (ethyl acetate–hexane), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.38 (6H, s), 4.26 (2H, s), 7.20 (2H, d, *J*=5.9 Hz), 7.24 (1H, s), 7.60 (2H, s), 8.56 (2H, d, *J*=5.9 Hz). *Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.83; H, 6.73; N, 6.18.

**1-(3,4-Dimethoxyphenyl)-2-(4-pyridyl)ethanone (4t)** This compound was prepared from **2q** as described in the synthesis of **4l** as a solid, yield 29%, mp 110–111 °C (ethyl acetate–hexane), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.94 (3H, s), 3.97 (3H, s), 4.26 (2H, s), 6.91 (1H, d, *J*=8.4 Hz), 7.22 (2H, d, *J*=5.9 Hz), 7.55 (1H, d, *J*=2.0 Hz), 7.64 (1H, dd, *J*=8.4, 2.0 Hz), 8.56 (2H,

d,  $J=5.9$  Hz). *Anal.* Calcd for  $C_{15}H_{15}NO_3$ : C, 70.02; H, 5.88; N, 5.44. Found: C, 69.97; H, 5.81; N, 5.47.

**1-(1,3-Benzodioxol-5-yl)-2-(4-pyridyl)ethanone (4u)** This compound was prepared from **2r** as described in the synthesis of **4l** as a solid, yield 36%, mp 126–127 °C (ethyl acetate–isopropyl ether),  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 4.21 (2H, s), 6.07 (2H, s), 6.87 (1H, d,  $J=8.2$  Hz), 7.20 (2H, d,  $J=6.0$  Hz), 7.46 (1H, d,  $J=1.7$  Hz), 7.61 (1H, dd,  $J=8.2, 1.7$  Hz), 8.56 (2H, d,  $J=6.0$  Hz). *Anal.* Calcd for  $C_{14}H_{11}NO_3$ : C, 69.70; H, 4.60; N, 5.81. Found: C, 69.76; H, 4.53; N, 5.78.

**1-[4-(1,1-Dimethylethyl)phenyl]-2-(3-pyridyl)ethanone (4v)** This compound was prepared from **2n** and 3-methylpyridine as described in the synthesis of **4l** as an oil, yield 28%,  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.34 (9H, s), 4.28 (2H, s), 7.22–7.31 (1H, m), 7.50 (2H, d,  $J=8.4$  Hz), 7.56–7.65 (1H, m), 7.94 (2H, d,  $J=8.4$  Hz), 8.48–8.55 (2H, m). *Anal.* Calcd for  $C_{17}H_{19}NO$ : C, 80.60; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.45; N, 5.41.

**1-(3,5-Dimethylphenyl)-2-(3-pyridyl)ethanone (4w)** This compound was prepared from **2p** and 3-methylpyridine as described in the synthesis of **4l** as an oil, yield 11%,  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.38 (6H, s), 4.27 (2H, s), 7.24–7.30 (2H, m), 7.58–7.63 (3H, m), 8.50–8.52 (2H, m). *Anal.* Calcd for  $C_{15}H_{15}NO$ : C, 79.97; H, 6.71; N, 6.22. Found: C, 79.89; H, 6.72; N, 6.13.

**2-Bromo-1-(4-ethylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5l)** Bromine (1.1 ml, 22 mmol) was added dropwise to a solution of **4l** (5.0 g, 22 mmol) in acetic acid (22 ml) and the mixture was stirred for 3 h at 80 °C. The solvent was removed *in vacuo* and ethyl acetate was added to the residue. The resulting crystals were collected by filtration and washed with ethyl acetate to afford 6.1 g (yield 71%) of **5l** as a solid,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 1.22 (3H, t,  $J=7.6$  Hz), 2.72 (2H, q,  $J=7.6$  Hz), 6.38 (1H, br s), 7.29 (1H, s), 7.45 (2H, d,  $J=8.1$  Hz), 8.07 (2H, d,  $J=8.1$  Hz), 8.15 (2H, d,  $J=6.2$  Hz), 8.94 (2H, d,  $J=6.2$  Hz). *Anal.* Calcd for  $C_{15}H_{14}BrNO \cdot HBr \cdot 0.5H_2O$ : C, 45.71; H, 4.09; N, 3.55. Found: C, 45.86; H, 3.99; N, 3.48.

**2-Bromo-1-(4-propylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5m)** This compound was prepared from **4m** as described in the synthesis of **5l** as a solid, yield 90%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 0.91 (3H, t,  $J=7.1$  Hz), 1.53–1.74 (2H, m), 2.67 (2H, t,  $J=7.3$  Hz), 5.14 (1H, br s), 7.25 (1H, s), 7.42 (2H, t,  $J=7.1$  Hz), 8.06 (2H, d,  $J=7.1$  Hz), 8.10 (2H, d,  $J=5.3$  Hz), 8.91 (2H, d,  $J=5.3$  Hz). *Anal.* Calcd for  $C_{16}H_{16}BrNO \cdot HBr$ : C, 48.15; H, 4.29; N, 3.51. Found: C, 48.04; H, 4.19; N, 3.43.

**2-Bromo-1-(4-butylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5n)** This compound was prepared from **4n** as described in the synthesis of **5l** as a solid, yield 88%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 0.91 (3H, t,  $J=7.3$  Hz), 1.22–1.43 (2H, m), 1.51–1.69 (2H, m), 2.69 (2H, t,  $J=7.5$  Hz), 6.12 (1H, br s), 7.29 (1H, s), 7.43 (2H, t,  $J=8.1$  Hz), 8.07 (2H, d,  $J=8.1$  Hz), 8.18 (2H, d,  $J=5.9$  Hz), 8.96 (2H, d,  $J=5.9$  Hz). *Anal.* Calcd for  $C_{17}H_{19}BrNO \cdot HBr \cdot 1.5H_2O$ : C, 46.39; H, 5.04; N, 3.18. Found: C, 46.61; H, 5.26; N, 3.05.

**2-Bromo-1-[4-(1-methylethyl)phenyl]-2-(4-pyridyl)ethanone Hydrobromide (5o)** This compound was prepared from **4o** as described in the synthesis of **5l** as a solid, yield 93%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 1.24 (6H, d,  $J=6.6$  Hz), 2.92–3.09 (1H, m), 5.75 (1H, br s), 7.27 (1H, s), 7.48 (2H, d,  $J=8.2$  Hz), 8.08 (2H, d,  $J=8.2$  Hz), 8.13 (2H, d,  $J=6.7$  Hz), 8.93 (2H, d,  $J=6.7$  Hz). *Anal.* Calcd for  $C_{16}H_{16}BrNO \cdot HBr$ : C, 48.15; H, 4.29; N, 3.51. Found: C, 48.15; H, 4.23; N, 3.34.

**2-Bromo-1-[4-(*N,N*-dimethylamino)phenyl]-2-(4-pyridyl)ethanone Dihydrobromide (5q)** Bromine (0.20 ml, 4.2 mmol) was added dropwise to a solution of **4q** (1.0 g, 4.2 mmol) in acetic acid (5 ml) and 30% hydrogen bromide acetic acid solution (1.23 g, 4.6 mmol) and the mixture was stirred for 3 h at 80 °C. The precipitate was collected by filtration and washed with ethyl acetate to afford 1.0 g (yield 50%) of **5q** as a solid,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 3.07 (6H, s), 6.24 (2H, br s), 6.78 (2H, d,  $J=9.0$  Hz), 7.20 (1H, s), 7.97 (2H, d,  $J=9.0$  Hz), 8.22 (2H, d,  $J=6.6$  Hz), 8.96 (2H, d,  $J=6.6$  Hz). *Anal.* Calcd for  $C_{15}H_{15}BrN_2O \cdot 1.5H_2O$ : C, 35.46; H, 3.97; N, 5.51. Found: C, 35.64; H, 4.03; N, 5.34.

**2-Bromo-1-(3,4-dimethylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5r)** This compound was prepared from **4r** as described in the synthesis of **5l** as a solid, yield 94%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 2.33 (6H, s), 7.32 (1H, s), 7.37 (2H, d,  $J=7.7$  Hz), 7.85–7.96 (2H, m), 8.20 (2H, d,  $J=6.8$  Hz), 8.97 (2H, d,  $J=6.8$  Hz), 1H hidden. *Anal.* Calcd for  $C_{15}H_{14}BrNO \cdot HBr$ : C, 46.78; H, 3.93; N, 3.64. Found: C, 46.51; H, 3.94; N, 3.43.

**2-Bromo-1-(3,5-dimethylphenyl)-2-(4-pyridyl)ethanone Hydrobromide (5s)** This compound was prepared from **4s** as described in the synthesis of **5l** as a solid, yield 81%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 2.38 (6H, s), 5.71 (1H, br s), 7.28 (1H, s), 7.38 (1H, s), 7.77 (2H, s), 8.16 (2H, d,  $J=5.5$  Hz), 8.95 (2H, d,  $J=5.5$  Hz). *Anal.* Calcd for  $C_{15}H_{14}BrNO \cdot HBr$ : C, 46.78; H, 3.93; N, 3.64. Found: C, 46.68; H, 4.22; N, 3.40.

**2-Bromo-1-(3,4-dimethoxyphenyl)-2-(4-pyridyl)ethanone Hydrobro-**

**mid (5t)** This compound was prepared from **4t** as described in the synthesis of **5l** as a solid, yield 79%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 3.85 (3H, s), 3.89 (3H, s), 4.61 (1H, br s), 7.14 (1H, d,  $J=8.4$  Hz), 7.28 (1H, s), 7.57 (1H, d,  $J=1.8$  Hz), 7.86 (1H, dd,  $J=8.4, 1.8$  Hz), 8.01 (2H, d,  $J=6.2$  Hz), 8.85 (2H, d,  $J=6.2$  Hz). *Anal.* Calcd for  $C_{15}H_{14}BrNO_3 \cdot HBr \cdot 0.2H_2O$ : C, 42.82; H, 3.69; N, 3.33. Found: C, 42.81; H, 3.81; N, 3.24.

**1-(1,3-Benzodioxol-5-yl)-2-bromo-2-(4-pyridyl)ethanone Hydrobromide (5u)** This compound was prepared from **4u** as described in the synthesis of **5l** as a solid, yield 91%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 5.02 (1H, br s), 6.19 (2H, s), 7.13 (1H, d,  $J=8.3$  Hz), 7.24 (1H, s), 7.60 (1H, d,  $J=1.5$  Hz), 7.82 (1H, dd,  $J=8.3, 1.5$  Hz), 8.18 (2H, d,  $J=7.5$  Hz), 8.92 (2H, d,  $J=7.5$  Hz). *Anal.* Calcd for  $C_{14}H_{10}BrNO_3 \cdot HBr \cdot 0.2H_2O$ : C, 41.55; H, 2.84; N, 3.46. Found: C, 41.60; H, 2.92; N, 3.37.

**2-Bromo-1-(4-(1,1-dimethylethyl)phenyl)-2-(3-pyridyl)ethanone Hydrobromide (5v)** This compound was prepared from **4v** as described in the synthesis of **5l** as a solid, yield 66%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 1.36 (9H, s), 4.53 (1H, br s), 7.25 (1H, s), 7.63 (2H, d,  $J=8.5$  Hz), 7.94–8.08 (1H, m), 8.09 (2H, d,  $J=8.5$  Hz), 8.57–8.71 (1H, m), 8.84–8.93 (1H, m), 9.04–9.13 (1H, m). *Anal.* Calcd for  $C_{16}H_{16}BrNO \cdot HBr \cdot H_2O$ : C, 46.07; H, 4.59; N, 3.36. Found: C, 46.19; H, 4.22; N, 2.99.

**2-Bromo-1-(3,5-dimethylphenyl)-2-(3-pyridyl)ethanone Hydrobromide (5w)** This compound was prepared from **4w** as described in the synthesis of **5l** as a solid, yield 92%,  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 2.38 (6H, s), 6.45 (1H, br s), 7.28 (1H, s), 7.37 (1H, s), 7.78 (2H, s), 8.01–8.08 (1H, m), 8.65–8.69 (1H, m), 8.89–8.92 (1H, m), 9.10–9.11 (1H, m). *Anal.* Calcd for  $C_{15}H_{14}BrNO \cdot HBr \cdot 0.5H_2O$ : C, 45.71; H, 4.09; N, 3.55. Found: C, 45.67; H, 3.95; N, 3.49.

**[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]amine (6d)** Thiourea (3.3 g, 46 mmol) was added to a mixture of 4'-methoxyphenacyl bromide (10 g, 44 mmol) in acetonitrile (260 ml). The resulting solution was refluxed for 3 h. The solvent was removed *in vacuo* and aqueous sodium hydrogen carbonate was added to the residue. The precipitate was collected by filtration and the resulting solid was washed with water and ether successively. The crude crystals were recrystallized from ethanol to afford 6.5 g (yield 73%) of **6d** as a solid, mp 203–204 °C (ethanol),  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 3.77 (3H, s), 6.80 (1H, s), 6.91 (2H, d,  $J=8.8$  Hz), 6.98 (2H, br s), 7.72 (2H, d,  $J=8.8$  Hz). *Anal.* Calcd for  $C_{10}H_{10}N_2OS$ : C, 58.23; H, 4.89; N, 13.58. Found: C, 58.08; H, 4.86; N, 13.91.

***N*-[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]methylamine (6e)** *N*-Methylthiourea (3.8 g, 43 mmol) was added to a mixture of **5a** (15 g, 39 mmol) in acetonitrile (200 ml) and then triethylamine (5.7 ml, 41 mmol) was added to the mixture. The resulting solution was refluxed for 3 h. The solvent was removed *in vacuo* and aqueous sodium hydrogen carbonate was added to the residue. The precipitate was collected by filtration and the resulting solid was washed with water and ether successively. The crude crystals were recrystallized from ethanol to afford 11 g (yield 88%) of **6e** as a solid, mp 175–177 °C (ethyl acetate),  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 2.88 (3H, d,  $J=4.8$  Hz), 3.78 (3H, s), 6.92 (2H, d,  $J=8.4$  Hz), 7.08 (2H, d,  $J=6.0$  Hz), 7.36 (2H, d,  $J=8.4$  Hz), 7.91 (1H, q,  $J=4.8$  Hz), 8.38 (2H, d,  $J=6.0$  Hz). *Anal.* Calcd for  $C_{16}H_{15}N_3OS \cdot 0.5H_2O$ : C, 62.72; H, 5.26; N, 13.71. Found: C, 62.66; H, 5.05; N, 14.07.

**[4-(4-Ethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6n)** This compound was prepared from **5l** as described in the synthesis of **6e** as a solid, yield 71%, mp 285–288 °C (pyridine),  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 1.20 (3H, t,  $J=7.5$  Hz), 2.62 (2H, q,  $J=7.5$  Hz), 7.08 (2H, d,  $J=6.2$  Hz), 7.17 (2H, d,  $J=8.1$  Hz), 7.32 (2H, d,  $J=8.1$  Hz), 7.40 (2H, br s), 8.37 (2H, d,  $J=6.2$  Hz). *Anal.* Calcd for  $C_{16}H_{15}N_3S$ : C, 68.30; H, 5.37; N, 14.93. Found: C, 68.14; H, 5.40; N, 15.09.

**[4-(4-Propylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6o)** This compound was prepared from **5m** as described in the synthesis of **6e** as a solid, yield 94%, mp 240–242 °C (ethanol),  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 0.91 (3H, t,  $J=7.3$  Hz), 1.50–1.72 (2H, m), 2.57 (2H, t,  $J=7.9$  Hz), 7.08 (2H, d,  $J=4.9$  Hz), 7.16 (2H, d,  $J=7.9$  Hz), 7.31 (2H, d,  $J=7.9$  Hz), 7.42 (2H, br s), 8.38 (2H, d,  $J=4.9$  Hz). *Anal.* Calcd for  $C_{17}H_{17}N_3S$ : C, 69.12; H, 5.80; N, 14.22. Found: C, 68.86; H, 5.82; N, 14.25.

**[4-(4-Butylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6p)** This compound was prepared from **5n** as described in the synthesis of **6e** as a solid, yield 63%, mp 204–206 °C (ethanol),  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 0.91 (3H, t,  $J=7.1$  Hz), 1.24–1.43 (2H, m), 1.49–1.66 (2H, m), 2.59 (2H, t,  $J=7.7$  Hz), 7.07 (2H, d,  $J=6.0$  Hz), 7.15 (2H, d,  $J=7.9$  Hz), 7.31 (2H, d,  $J=7.9$  Hz), 7.36 (2H, br s), 8.37 (2H, d,  $J=6.0$  Hz). *Anal.* Calcd for  $C_{18}H_{19}N_3S \cdot 0.5H_2O$ : C, 67.89; H, 6.33; N, 13.20. Found: C, 67.98; H, 6.13; N, 13.23.

**[4-[4-(1-Methylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6q)**



This compound was prepared from **5o** as described in the synthesis of **6e** as a solid, yield 77%, mp 267–269 °C (pyridine), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.22 (6H, d, *J*=6.9 Hz), 2.82–2.98 (1H, m), 7.10 (2H, d, *J*=6.1 Hz), 7.21 (2H, d, *J*=8.3 Hz), 7.34 (2H, d, *J*=8.3 Hz), 7.40 (2H, br s), 8.39 (2H, d, *J*=6.1 Hz). *Anal.* Calcd for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>S: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.08; H, 5.52; N, 14.25.

**[4-(*N,N*-Dimethylamino)phenyl-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6s)** This compound was prepared from **5q** as described in the synthesis of **6e** as a solid, yield 54%, mp 309–311 °C (pyridine), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.93 (6H, s), 6.65 (2H, d, *J*=9.0 Hz), 7.10 (2H, d, *J*=6.2 Hz), 7.25 (2H, d, *J*=9.0 Hz), 7.32 (2H, br s), 8.36 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>S: C, 64.84; H, 5.44; N, 18.90. Found: C, 64.49; H, 5.40; N, 18.82.

**[4-(3,4-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6t)** This compound was prepared from **5r** as described in the synthesis of **6e** as a solid, yield 96%, mp 248–250 °C (pyridine), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.19 (3H, s), 2.23 (3H, s), 7.05–7.11 (4H, m), 7.24 (1H, s), 7.37 (2H, br s), 8.36 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>S: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.62; H, 5.39; N, 15.13.

**[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6u)** This compound was prepared from **5s** as described in the synthesis of **6e** as a solid, yield 55%, mp 242–244 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.22 (6H, s), 6.97 (1H, s), 7.01 (2H, s), 7.07 (2H, d, *J*=6.2 Hz), 7.39 (2H, br s), 8.37 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>S: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.17; H, 5.34; N, 14.70.

**[4-(3,4-Dimethoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6v)** This compound was prepared from **5t** as described in the synthesis of **6e** as a solid, yield 70%, mp 218–219 °C (pyridine), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 3.68 (3H, s), 3.81 (3H, s), 6.90–6.99 (2H, m), 7.02 (1H, s), 7.27 (2H, d, *J*=6.8 Hz), 7.74 (2H, br s), 8.43 (2H, d, *J*=6.8 Hz). *Anal.* Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.45; H, 4.40; N, 13.02.

**[4-(1,3-Benzodioxol-5-yl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6w)** This compound was prepared from **5u** as described in the synthesis of **6e** as a solid, yield 79%, mp 273–275 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 6.04 (2H, s), 6.83–6.92 (3H, m), 7.09 (2H, d, *J*=6.2 Hz), 7.37 (2H, br s), 8.39 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.67; H, 3.81; N, 14.24.

**[4-[4-(1,1-Dimethylethyl)phenyl]-5-(3-pyridyl)-1,3-thiazol-2-yl]amine (6x)** This compound was prepared from **5v** as described in the synthesis of **6e** as a solid, yield 82%, mp 239–241 °C (ethanol–ethyl acetate), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.27 (9H, s), 7.21 (2H, br s), 7.30 (4H, s), 7.34 (1H, dd, *J*=8.2, 4.9 Hz), 7.62 (1H, ddd, *J*=8.2, 2.2, 1.8 Hz), 8.38 (1H, d, *J*=2.2 Hz), 8.41 (1H, dd, *J*=4.9, 1.8 Hz). *Anal.* Calcd for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>S: C, 69.87; H, 6.19; N, 13.58. Found: C, 69.75; H, 6.17; N, 13.43.

**[4-(3,5-Dimethylphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine (6y)** This compound was prepared from **5w** as described in the synthesis of **6e** as a solid, yield 52%, mp 237–240 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.17 (6H, s), 6.91 (1H, s), 6.97 (2H, s), 7.22 (2H, br s), 7.27–7.33 (1H, m), 7.55–7.59 (1H, m), 8.36–8.42 (2H, m). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>OS: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.03; H, 5.25; N, 14.87.

**[4-(4-Hydroxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]amine (6z)** A solution of **6a** (7.3 g) in 47% hydrobromic acid (60 ml) was refluxed for 5 h. The resulting mixture was cooled with an ice bath and neutralized with 8*N* aqueous sodium hydroxide. The precipitate was collected by filtration and washed with water. The crude crystals were washed with ethanol and dried to afford 7.09 g (28 mmol, yield quant.) of **6z** as a solid, mp 323–326 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 6.76 (2H, d, *J*=8.8 Hz), 7.22 (2H, d, *J*=6.6 Hz), 7.26 (2H, d, *J*=8.8 Hz), 7.69 (2H, br s), 8.41 (2H, d, *J*=6.6 Hz), 9.74 (1H, br s). *Anal.* Calcd for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>OS·3H<sub>2</sub>O: C, 52.00; H, 5.30; N, 12.99. Found: C, 51.64; H, 4.99; N, 12.96.

**Ethyl [4-(4-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetate (6aa)** This compound was prepared from ethyl thiocarbonylacetate<sup>31)</sup> as described in the synthesis of **6a** as an oil, yield 77%, <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.33 (3H, t, *J*=7.0 Hz), 3.82 (3H, s), 4.12 (2H, s), 4.27 (2H, q, *J*=7.0 Hz), 6.86 (2H, d, *J*=9.0 Hz), 7.25 (2H, d, *J*=6.2 Hz), 7.41 (2H, d, *J*=9.0 Hz), 8.54 (2H, d, *J*=6.2 Hz).

***N*-[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]acetamide (7d)** A solution of ethyl cyanoacetate (1.2 g, 10 mmol) and **6d** (2.1 g, 10 mmol) in acetic acid (10 ml) was refluxed for 38 h. The solvent was removed *in vacuo* and the residue was treated with aqueous sodium hydrogen carbonate. The crude crystals were collected by filtration and washed, and then recrystallized from ethanol to afford 4.2 g (yield 47%) of **7d** as a solid, mp 192–193 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.16 (3H, s), 3.79 (3H, s), 6.98 (2H, d, *J*=8.8 Hz), 7.41 (1H, s), 7.82 (2H, d, *J*=8.8 Hz), 12.19 (1H, br s). *Anal.*

Calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.06; H, 4.69; N, 11.28.

***N*-[4-(4-Methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]-*N*-methylacetamide (7e)** Acetyl chloride (3.8 g, 48 mmol) was added to a solution of **6e** (10 g, 32 mmol) and 4-dimethylaminopyridine (1.2 g, 9.6 mmol) in *N,N*-dimethylacetamide (50 ml) and the resulting mixture was stirred at 80 °C for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and extracted with ethyl acetate. Extracts were washed with brine, dried and concentrated to give a solid. The crude crystals were recrystallized from ethanol to afford 7.0 g (yield 65%) of **7e** as a solid, mp 180–181 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.43 (3H, s), 3.71 (3H, s), 3.78 (3H, s), 6.94 (2H, d, *J*=8.4 Hz), 7.28 (2H, d, *J*=5.9 Hz), 7.40 (2H, d, *J*=8.4 Hz), 8.52 (2H, d, *J*=5.9 Hz). *Anal.* Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.40; H, 5.01; N, 12.18.

***N*-[4-(4-Ethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7n)** This compound was prepared from **6n** as described in the synthesis of **7e** as a solid, yield 47%, mp 294–295 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.20 (3H, t, *J*=7.5 Hz), 2.19 (3H, s), 2.63 (2H, q, *J*=7.5 Hz), 7.21 (2H, d, *J*=8.1 Hz), 7.27 (2H, d, *J*=6.0 Hz), 7.36 (2H, d, *J*=8.1 Hz), 8.50 (2H, d, *J*=6.0 Hz), 12.45 (1H, br s). *Anal.* Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>OS·0.1H<sub>2</sub>O: C, 66.48; H, 5.33; N, 12.92. Found: C, 66.41; H, 5.03; N, 12.88.

***N*-[4-(4-Propylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7o)** This compound was prepared from **6o** as described in the synthesis of **7e** as a solid, yield 57%, mp 256–258 °C (ethyl acetate), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 0.91 (3H, t, *J*=7.3 Hz), 1.50–1.72 (2H, m), 2.19 (3H, s), 2.57 (2H, t, *J*=7.3 Hz), 7.18 (2H, d, *J*=8.1 Hz), 7.26 (2H, d, *J*=6.2 Hz), 7.35 (2H, d, *J*=8.1 Hz), 8.50 (2H, d, *J*=6.2 Hz), 12.42 (1H, br s). *Anal.* Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>OS·0.2H<sub>2</sub>O: C, 66.91; H, 5.73; N, 12.32. Found: C, 66.82; H, 5.70; N, 12.26.

***N*-[4-(4-Butylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7p)** This compound was prepared from **6p** as described in the synthesis of **7e** as a solid, yield 57%, mp 259–261 °C (ethyl acetate), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 0.91 (3H, t, *J*=7.1 Hz), 1.25–1.43 (2H, m), 1.46–1.66 (2H, m), 2.19 (3H, s), 2.59 (2H, t, *J*=7.5 Hz), 7.18 (2H, d, *J*=8.1 Hz), 7.25 (2H, d, *J*=6.2 Hz), 7.35 (2H, d, *J*=8.1 Hz), 8.49 (2H, d, *J*=6.2 Hz), 12.42 (1H, br s). *Anal.* Calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>OS: C, 68.35; H, 6.02; N, 11.96. Found: C, 68.10; H, 5.81; N, 11.82.

***N*-[4-[4-(1-Methylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7q)** This compound was prepared from **6q** as described in the synthesis of **7e** as a solid, yield 62%, mp 295–297 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.22 (6H, d, *J*=7.0 Hz), 2.19 (3H, s), 2.82–2.99 (1H, m), 7.19–7.30 (4H, m), 7.37 (2H, d, *J*=8.1 Hz), 8.51 (2H, d, *J*=5.9 Hz), 12.42 (1H, br s). *Anal.* Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>OS: C, 67.63; H, 5.68; N, 12.45. Found: C, 67.66; H, 5.66; N, 12.55.

***N*-[4-[4-(*N,N*-Dimethylamino)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7s)** A 4*N* hydrogen chloride in ethyl acetate (0.37 ml) was added to a solution of **6s** (0.40 g, 1.4 mmol) in *N,N*-dimethylacetamide (4.0 ml) and acetyl chloride (0.16 g, 2.0 mmol) was added to the mixture. The resulting mixture was stirred at 80 °C for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was washed with water and dried. The crude crystals were recrystallized from ethanol to afford 0.26 g (yield 56%) of **7s** as a solid, mp 289–291 °C, <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.18 (3H, s), 2.93 (6H, s), 6.67 (2H, d, *J*=8.8 Hz), 7.24–7.32 (4H, m), 8.48 (2H, d, *J*=6.3 Hz), 12.34 (1H, br s). *Anal.* Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>OS·0.2H<sub>2</sub>O: C, 63.21; H, 5.42; N, 16.38. Found: C, 63.08; H, 5.40; N, 16.42.

***N*-[4-(3,4-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7t)** This compound was prepared from **6t** as described in the synthesis of **7e** as a solid, yield 29%, mp 248–250 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.19 (6H, s), 2.24 (3H, s), 7.10 (2H, s), 7.22–7.30 (3H, m), 8.49 (2H, d, *J*=5.9 Hz), 12.43 (1H, br s). *Anal.* Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>OS: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.66; H, 5.28; N, 13.08.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7u)** This compound was prepared from **6u** as described in the synthesis of **7e** as a solid, yield 29%, mp 284–286 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.19 (3H, s), 2.22 (6H, s), 7.00 (1H, s), 7.04 (2H, s), 7.26 (2H, d, *J*=6.2 Hz), 8.50 (2H, d, *J*=6.2 Hz), 12.43 (1H, br s). *Anal.* Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>OS·0.1H<sub>2</sub>O: C, 66.48; H, 5.33; N, 12.92. Found: C, 66.35; H, 5.21; N, 13.07.

***N*-[4-(3,4-Dimethoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7v)** This compound was prepared from **6v** as described in the synthesis of **7e** as a solid, yield 62%, mp 265–267 °C (ethanol), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 2.19 (3H, s), 3.62 (3H, s), 3.77 (3H, s), 6.94 (2H, s), 7.02 (1H, s), 7.29 (2H, d, *J*=5.7 Hz), 8.52 (2H, d, *J*=5.7 Hz), 12.45 (1H, br s). *Anal.* Calcd for

$C_{18}H_{17}N_3O_3S$ : C, 60.83; H, 4.82; N, 11.82. Found: C, 60.70; H, 4.73; N, 11.83.

***N*-[4-(1,3-Benzodioxol-5-yl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (7w)** This compound was prepared from **6w** as described in the synthesis of **7e** as a solid, yield 68%, mp 295–296 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.19 (3H, s), 6.05 (2H, s), 6.86–6.96 (3H, m), 7.27 (2H, d,  $J=6.0$  Hz), 8.51 (2H, d,  $J=6.0$  Hz), 12.40 (1H, brs). *Anal.* Calcd for  $C_{17}H_{13}N_3O_3S$ : C, 60.17; H, 3.86; N, 12.38. Found: C, 60.04; H, 3.88; N, 12.44.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide (7x)** This compound was prepared from **6r** and propionyl chloride as described in the synthesis of **7a** as a solid, yield 74%, mp 295–297 °C (ethyl acetate–ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.13 (3H, t,  $J=7.5$  Hz), 1.29 (9H, s), 2.49 (2H, q,  $J=7.5$  Hz), 7.28 (2H, d,  $J=6.2$  Hz), 7.38 (4H, s), 8.51 (2H, d,  $J=6.2$  Hz), 12.41 (1H, brs). *Anal.* Calcd for  $C_{21}H_{23}N_3O_3S$ : C, 69.01; H, 6.34; N, 11.50. Found: C, 68.88; H, 6.36; N, 11.50.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]cyclopentanecarboxamide (7y)** This compound was prepared from **6r** and cyclopentanecarbonyl chloride as described in the synthesis of **7e** as a solid, yield 74%, mp 309–311 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.29 (9H, s), 1.53–2.01 (8H, m), 2.91–3.05 (1H, m), 7.27 (2H, d,  $J=6.2$  Hz), 7.38 (4H, s), 8.52 (2H, d,  $J=6.2$  Hz), 12.40 (1H, brs). *Anal.* Calcd for  $C_{24}H_{27}N_3O_3S$ : C, 71.08; H, 6.71; N, 10.36. Found: C, 71.00; H, 6.76; N, 10.26.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]benzamide (7z)** This compound was prepared from **6r** and benzoyl chloride as described in the synthesis of **7e** as a solid, yield 74%, mp 292–294 °C (ethyl acetate–ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.31 (9H, s), 7.33 (2H, d,  $J=6.1$  Hz), 7.40 (2H, d,  $J=8.9$  Hz), 7.48 (2H, d,  $J=8.9$  Hz), 7.52–7.72 (3H, m), 8.16 (2H, d,  $J=7.0$  Hz), 8.55 (2H, d,  $J=6.1$  Hz), 12.39 (1H, brs). *Anal.* Calcd for  $C_{25}H_{23}N_3O_3S$ : C, 72.61; H, 5.61; N, 10.16. Found: C, 72.53; H, 5.45; N, 10.28.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide (7aa)** This compound was prepared from **6r** and nicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 73%, mp 326–328 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.31 (9H, s), 7.32 (2H, d,  $J=5.9$  Hz), 7.42 (4H, s), 7.59 (1H, dd,  $J=8.1, 4.8$  Hz), 8.47 (1H, dd,  $J=8.1, 2.2$  Hz), 8.54 (2H, d,  $J=5.9$  Hz), 8.81 (1H, d,  $J=4.8$  Hz), 9.26 (1H, d,  $J=2.2$  Hz), 12.39 (1H, br s). *Anal.* Calcd for  $C_{24}H_{22}N_4O_3S$ : C, 69.54; H, 5.35; N, 13.52. Found: C, 69.51; H, 5.30; N, 13.82.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]isonicotinamide (7ab)** This compound was prepared from **6r** and isonicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 74%, mp 326–329 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.31 (9H, s), 7.32 (2H, d,  $J=6.2$  Hz), 7.42 (4H, s), 8.03 (2H, d,  $J=6.2$  Hz), 8.55 (2H, d,  $J=6.2$  Hz), 8.83 (2H, d,  $J=6.2$  Hz), 12.40 (1H, brs). *Anal.* Calcd for  $C_{24}H_{22}N_4O_3S$ : C, 69.54; H, 5.35; N, 13.52. Found: C, 69.53; H, 5.32; N, 13.66.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide (7ac)** This compound was prepared from **6u** and propionyl chloride as described in the synthesis of **7e** as a solid, yield 67%, mp 291–293 °C (ethanol),  $^1H$ -NMR (CDCl $_3$ )  $\delta$ : 1.04 (3H, t,  $J=7.6$  Hz), 2.01 (2H, q,  $J=7.6$  Hz), 2.27 (6H, s), 7.01 (1H, s), 7.08 (2H, s), 7.22–7.25 (2H, m), 8.50–8.53 (2H, m), 10.60 (1H, brs). *Anal.* Calcd for  $C_{19}H_{19}N_3O_3S$ : C, 67.63; H, 5.68; N, 12.45. Found: C, 67.57; H, 5.52; N, 12.48.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]cyclopentanecarboxamide (7ad)** This compound was prepared from **6u** and cyclopentanecarbonyl chloride as described in the synthesis of **7e** as a solid, yield 59%, mp 275–278 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.52–1.98 (8H, m), 2.21 (6H, s), 2.92–3.00 (1H, m), 7.00 (1H, s), 7.05 (2H, s), 7.25–7.28 (2H, m), 8.49–8.52 (2H, m), 12.43 (1H, brs). *Anal.* Calcd for  $C_{22}H_{23}N_3O_3S$ : C, 70.00; H, 6.14; N, 11.13. Found: C, 69.76; H, 6.05; N, 11.13.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]benzamide (7ae)** This compound was prepared from **6u** and benzoyl chloride as described in the synthesis of **7e** as a solid, yield 26%, mp 285–286 °C (ethanol),  $^1H$ -NMR (CDCl $_3$ )  $\delta$ : 2.23 (6H, s), 6.93 (1H, s), 7.03 (2H, s), 7.26–7.29 (2H, m), 7.43–7.63 (3H, m), 7.87–7.91 (2H, m), 8.50–8.54 (2H, m), 10.37 (1H, brs). *Anal.* Calcd for  $C_{23}H_{19}N_3O_3S$ : C, 71.66; H, 4.97; N, 10.90. Found: C, 71.39; H, 4.91; N, 11.14.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide (7af)** This compound was prepared from **6u** and nicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 61%, mp 267–270 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.23 (6H, s), 7.03 (1H, s),

7.10 (2H, s), 7.32 (2H, d,  $J=6.0$  Hz), 7.58–7.65 (1H, m), 8.45–8.56 (3H, m), 8.81–8.84 (1H, m), 9.26–9.27 (1H, m), 13.21 (1H, brs). *Anal.* Calcd for  $C_{22}H_{18}N_4O_3S$ : C, 68.37; H, 4.69; N, 14.50. Found: C, 68.25; H, 4.57; N, 14.50.

***N*-[4-(3,5-Dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]isonicotinamide (7ag)** This compound was prepared from **6u** and isonicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 32%, mp 302–304 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.23 (6H, s), 7.02 (1H, s), 7.09 (2H, s), 7.31 (2H, d,  $J=6.2$  Hz), 8.03 (2H, d,  $J=6.2$  Hz), 8.53 (2H, d,  $J=5.9$  Hz), 8.83 (2H, d,  $J=5.9$  Hz), 13.29 (1H, brs). *Anal.* Calcd for  $C_{22}H_{18}N_4O_3S \cdot 0.2H_2O$ : C, 67.74; H, 4.75; N, 14.36. Found: C, 67.81; H, 4.72; N, 14.35.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide (7ah)** This compound was prepared from **6x** as described in the synthesis of **7e** as a solid, yield 67%, mp 228–230 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.28 (9H, s), 2.19 (3H, s), 7.35 (4H, s), 7.41 (1H, dd,  $J=7.7, 4.8$  Hz), 7.76 (1H, ddd,  $J=7.7, 2.2, 1.5$  Hz), 8.48 (1H, d,  $J=2.2$  Hz), 8.52 (1H, dd,  $J=4.8, 1.5$  Hz), 12.36 (1H, brs). *Anal.* Calcd for  $C_{20}H_{21}N_3O_3S \cdot 0.3H_2O$ : C, 67.31; H, 6.10; N, 11.77. Found: C, 67.31; H, 6.11; N, 11.53.

***N*-[4-[4-(1,1-Dimethylethyl)phenyl]-5-(3-pyridyl)-1,3-thiazol-2-yl]nicotinamide (7ai)** This compound was prepared from **6x** and nicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 63%, mp 251–253 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.29 (9H, s), 7.37 (2H, d,  $J=8.9$  Hz), 7.42 (2H, d,  $J=8.9$  Hz), 7.43 (1H, dd,  $J=7.7, 4.8$  Hz), 7.60 (1H, dd,  $J=8.0, 4.8$  Hz), 7.81 (1H, ddd,  $J=7.7, 2.2, 1.7$  Hz), 8.48 (1H, ddd,  $J=8.0, 2.1, 1.7$  Hz), 8.54 (1H, d,  $J=2.2$  Hz), 8.55 (1H, dd,  $J=4.8, 1.7$  Hz), 8.82 (1H, dd,  $J=4.8, 1.7$  Hz), 9.27 (1H, d,  $J=2.1$  Hz), 12.37 (1H, brs). *Anal.* Calcd for  $C_{24}H_{22}N_4O_3S$ : C, 69.54; H, 5.35; N, 13.52. Found: C, 69.47; H, 5.39; N, 13.46.

***N*-[4-(3,5-Dimethylphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide (7aj)** This compound was prepared from **6y** and acetyl chloride as described in the synthesis of **7e** as a solid, yield 71%, mp 288–289 °C (ethanol–ethyl acetate),  $^1H$ -NMR (CDCl $_3$ )  $\delta$ : 1.88 (3H, s), 2.23 (6H, s), 6.95 (1H, s), 7.04 (2H, s), 7.20–7.26 (1H, m), 7.61–7.67 (1H, m), 8.51–8.55 (1H, m), 8.60–8.61 (1H, m), 10.47 (1H, brs). *Anal.* Calcd for  $C_{18}H_{17}N_3O_3S$ : C, 66.85; H, 5.30; N, 12.99. Found: C, 66.64; H, 5.29; N, 12.84.

***N*-[4-(3,5-Dimethylphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]isonicotinamide (7ak)** This compound was prepared from **6y** and isonicotinoyl chloride hydrochloride as described in the synthesis of **7e** as a solid, yield 64%, mp 277–278 °C (ethanol),  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.20 (6H, s), 6.98 (1H, s), 7.07 (2H, s), 7.40–7.46 (1H, m), 7.55–7.64 (1H, m), 7.76–7.80 (1H, m), 8.45–8.53 (3H, m), 8.81 (1H, d,  $J=3.0$  Hz), 9.26 (1H, s), 13.15 (1H, brs). *Anal.* Calcd for  $C_{22}H_{18}N_4O_3S$ : C, 68.37; H, 4.69; N, 14.50. Found: C, 68.14; H, 4.53; N, 14.51.

**4-[2-(Acetylamino)-5-(4-pyridyl)-1,3-thiazol-4-yl]phenyl Acetate (9)** Acetyl chloride (10.0 g, 127 mmol) was added to a solution of **6z** (6.5 g, 25 mmol) and 4-dimethylaminopyridine (0.93 g, 7.6 mmol) in *N,N*-dimethylacetamide (50 ml), and the resulting mixture was stirred at 80 °C for 14 h. Aqueous sodium hydrogen carbonate was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was washed with water and dried. The crude crystals were recrystallized from ethanol to afford 5.33 g (yield 59%) of **9** as a solid, mp 254–257 °C,  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.20 (3H, s), 2.28 (3H, s), 7.14 (2H, d,  $J=8.8$  Hz), 7.28 (2H, d,  $J=6.0$  Hz), 7.47 (2H, d,  $J=8.8$  Hz), 8.52 (2H, d,  $J=6.0$  Hz), 12.47 (1H, brs). *Anal.* Calcd for  $C_{18}H_{15}N_3O_3S \cdot 0.2H_2O$ : C, 60.56; H, 4.35; N, 11.77. Found: C, 60.61; H, 4.23; N, 11.80.

***N*-[4-(4-Hydroxyphenyl)-5-(4-pyridinyl)-1,3-thiazol-2-yl]acetamide (10)** A mixture of **9** (5.0 g, 14 mmol) and potassium carbonate (2.2 g, 16 mmol) in methanol (500 ml) was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was treated with water. The mixture was acidified with 3 *N* hydrochloric acid and extracted with tetrahydrofuran and ethyl acetate. Extracts were washed with brine, dried and concentrated *in vacuo* to give a solid. The crude crystals were recrystallized from ethanol to afford 4.02 g (yield 91%) of **10** as a solid, mp 285–287 °C,  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.18 (3H, s), 6.74 (2H, d,  $J=8.8$  Hz), 7.25 (2H, d,  $J=8.8$  Hz), 7.26 (2H, d,  $J=5.9$  Hz), 8.49 (2H, d,  $J=5.9$  Hz), 9.68 (1H, brs), 12.47 (1H, brs). *Anal.* Calcd for  $C_{16}H_{13}N_3O_3S \cdot 0.7H_2O$ : C, 59.32; H, 4.48; N, 12.97. Found: C, 59.34; H, 4.75; N, 13.12.

***N*-[4-(4-Ethoxyphenyl)-5-(4-pyridinyl)-1,3-thiazol-2-yl]acetamide (11a)** A mixture of **10** (0.40 g, 1.3 mmol) and potassium butoxide (0.15 g, 1.4 mmol) in *N,N*-dimethylacetamide (4.0 ml) was stirred at 0 °C for 0.5 h. Ethyl iodide (0.22 g, 1.4 mmol) was added to the mixture at 0 °C and allowed to warm up to room temperature. The mixture was stirred at room tempera-

ture for 16 h and 3 N hydrochloric acid was added to the mixture. Aqueous sodium hydrogen carbonate was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was washed with water and dried. The solid was chromatographed on silica gel eluting with hexane-ethyl acetate (1 : 2) to give crude crystals, which were recrystallized from ethyl acetate to afford 0.08 g (yield 19%) of **11a** as a solid, mp 206–209 °C, <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.34 (3H, t, *J*=7.0 Hz), 2.45 (3H, s), 4.24 (2H, q, *J*=7.0 Hz), 6.75 (2H, d, *J*=6.2 Hz), 7.24–7.32 (4H, m), 8.50 (2H, d, *J*=6.2 Hz), 9.66 (1H, br s), 12.37 (1H, br s). *Anal.* Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.25; H, 4.99; N, 12.21.

**N-[4-(4-Butoxyphenyl)-5-(4-pyridinyl)-1,3-thiazol-2-yl]acetamide (11b)** This compound was prepared from butyl iodide as described in the synthesis of **11a** as a solid, yield 20%, mp 201–203 °C (ethyl acetate), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 0.96 (3H, t, *J*=7.1 Hz), 1.29–1.50 (2H, m), 1.66–1.84 (2H, m), 2.45 (3H, s), 4.20 (2H, t, *J*=7.5 Hz), 6.75 (2H, d, *J*=8.8 Hz), 7.27 (2H, d, *J*=5.9 Hz), 7.28 (2H, d, *J*=8.8 Hz), 8.51 (2H, d, *J*=5.9 Hz), 9.68 (1H, br s). *Anal.* Calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.05; H, 5.81; N, 11.50.

**4-(4-Methoxyphenyl)-2-methyl-5-(4-pyridyl)-1,3-thiazole (12)** A 2 N sodium hydroxide solution (8.5 ml, 17 mmol) was added to a solution of **6aa** (3.0 g, 8.5 mmol) in ethanol (8.5 ml) at room temperature and the resulting mixture was stirred for 2 h. The solvent was removed *in vacuo* and the residue was acidified with 3 N hydrochloric acid. The precipitate was collected by filtration and dried. The crystal was added to ethanol (100 ml) and the mixture was refluxed for 3 h. The solvent was removed *in vacuo* and the crude crystals were recrystallized from ethanol to afford 1.5 g (yield 56%) of **11** as a solid, mp 132–133 °C, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.76 (3H, s), 3.83 (3H, s), 6.86 (2H, d, *J*=9.0 Hz), 7.21 (2H, d, *J*=6.2 Hz), 7.41 (2H, d, *J*=9.0 Hz), 8.52 (2H, d, *J*=6.2 Hz). *Anal.* Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>OS·0.1H<sub>2</sub>O: C, 67.63; H, 5.04; N, 9.86. Found: C, 67.60; H, 4.99; N, 9.75.

**Human A<sub>1</sub>, A<sub>2A</sub>, and A<sub>3</sub> Receptor and Rat A<sub>3</sub> Binding Assay** Binding assay for A<sub>3</sub>AR was performed in 100 μl binding assay buffer (50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 10 mM MgCl<sub>2</sub>, 0.25 mM PMSF, 1 mg/ml pepstatin, 20 mg/ml leupeptin) containing 10 μg of membrane protein and 20 nM [<sup>3</sup>H]-NECA (Amersham Life Sciences, Inc., Tokyo) in the presence of various concentrations of compounds. Following incubation at room temperature for 1 h, the binding reaction was filtrated through the GF/C unifier (Packard Instrument Company, Tokyo) and washed three times with ice-cold 50 mM Tris-HCl (pH 7.5), using a Cell Harvester (Packard Instrument Company, Tokyo). The filter was dried and MicroScint-O was placed on the filter. Radioactivity retained on the filter was determined by Top-Count (Packard Instrument Company, Tokyo).

**IB-MECA Induced Plasma Protein Extravasation Assay** Male Sprague-Dawley rats (8 weeks old, CLEA Japan, Inc.) were used under light ether anesthesia. The back of the animal was shaved and intravenously injected with 1.0 ml of 0.5% Evans blue (Tokyo Chemical Industry Co., Ltd.) in saline. Immediately, each animal was injected intradermally with 50 μl of IB-MECA (10 μM) and 50 μl of vehicle (PBS), respectively. Thirty minutes after intradermal injections, rats were sacrificed and the dorsal skin was carefully removed, and the injection sites were excised with a cork borer (15 mm diameter). For dye recovery, the skin samples were placed in test tubes containing 2 ml of a mixture of 0.3% Na<sub>2</sub>SO<sub>4</sub> and acetone (3 : 7) at room temperature overnight. Plasma protein extravasation was quantitated by measuring the absorbance of Evans blue at 610 nm with a spectrophotometer (TR-1000T, CORONA ELECTRIC). The compounds were orally administered 1 h before IB-MECA intradermal injection.

**Antigen-Induced Rat Asthma Model. Animals, Sensitization and Antigen Challenge** Male Brown Norway rats (8 weeks old, Charles River Japan Inc., Yokohama, Japan) were sensitized by an intramuscular injection of 1 mg ovalbumin (OVA, Grade III, Sigma Chemical Co.) and 200 mg of aluminium hydroxide (Wako Pure Chemical Industries, Ltd.) in 1 ml of saline. At the same time, 1 ml of Bordetella pertussis vaccine (Wako Pure Chemical Industries, Ltd.) containing 1×10<sup>10</sup> heat-killed bacilli in saline was administered intraperitoneally as an adjuvant. Three weeks after sensitization, animals were placed in a box (20×21×13 cm) and exposed to aerosolized 1% OVA or saline for 5 min. The aerosol was generated with an ultrasonic nebulizer (Atom Medical Systems).

**Assessment of Airway Responsiveness** Airway responsiveness to acetylcholine was measured 23–30 h after antigen challenge. The rats were anesthetized with an intraperitoneal injection of pentobarbital sodium (50 mg/kg, Abbott Laboratories). A tracheal cannula, through which the rat was mechanically ventilated, was inserted *via* a tracheotomy. A cannula was also inserted into the external jugular vein. The rat was mechanically ventilated (2–3 ml/breath, 90 breaths/min, 10 cm H<sub>2</sub>O) (rodent ventilator

MODEL683, Harvard Apparatus). Pancuronium bromide (1 mg/kg, Sigma Chemicals Co.) was then administered intravenously and 1 min later, propranolol (1 mg/kg) was given intravenously. One minute after propranolol administration, the rat was given aerosolized saline for 15 s and baseline was decided. After 1.5 min, the rat was given aerosolized acetylcholine at an initial dose of 3 mg/ml and then 10, 30, 100 and 300 mg/ml for 15 s at 2-min intervals. The aerosol was generated with an ultrasonic nebulizer (Aerosonic MODEL5000D; Devilbiss). Intrapulmonary pressure was measured with a transducer and the response was measured as the peak increase above the baseline. Compound **7af** (10 mg/kg) and dexamethasone (0.01 mg/kg) were orally administered 1 h before and 7 h after antigen challenge.

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